VOLUME 44 NUMBER 2

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CONTENTS OF PREVIOUS NUMBER

JULY 1950. NUMBER 1

Reconstruction of the Floor of the Orbit by Bone Grafts. John Marquis Converse, M.D., and Byron Smith, M.D., New York.

Penetration of Chloramphenicol U. S. P. (Chloromycetin®) into the Eye. Irving H. Leopold, M.D.; Anna C. Nichols, M.S., and Adolph W. Vogel, M.D., Philadelphia.

Craniofacial Dysostosis (Crouzon's Disease): Report of Three Cases. Max S. Lahe, M.D., and John C. Koppinger, M.D., Omaha.

Corneal Response to Emetine Hydrochloride. Mortimer A. Lasky, M.D., Brooklyn.

The 1/2000 Field in Chiasmal Interference. Max Chamlin, M.D., and Leo M. Davidoff, M.D., New York.

Retinoblastoma: Analysis of Seventeen Autopsies. George R. Merrian Jr., M.D., New York.

Asymmetric Exophthalmos. Edward P. Dreecher, M.D., Berkeley, Calif., and William L. Benedict, M.D., Rochester, Minn.

A New Test for Function of the Macula Lutea. Max Goldschmidt, M.D., New York.

Torsion of the Eye on Oblique Gaze. Robert A. Moore, M.D., Delavan, Wis.

Clinical Notes:

Glioma of the Retina in Father and Child. Joseph Laval, M.D., New York.

Annual Reviews:

Strabismus: Review of the Literature. Harmon M. Burian, M.D., Boston.

News and Notes.

Obituaries:

Manuel A. da Silva, M.D.

Society Transactions:

College of Physicians of Philadelphia, Section on Ophthalmology.

Book Reviews.

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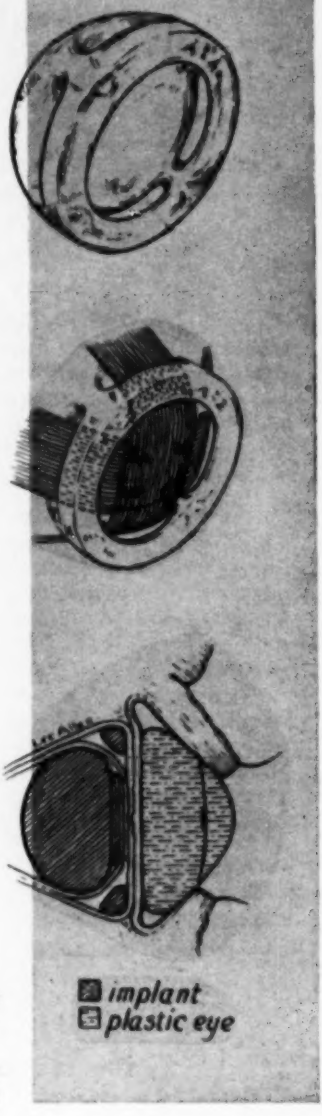

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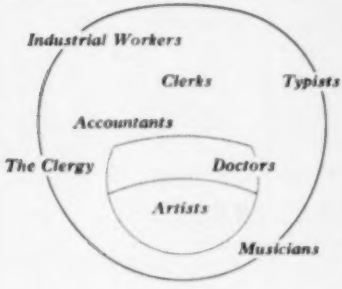

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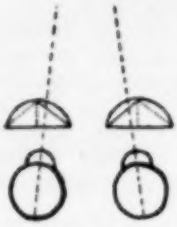

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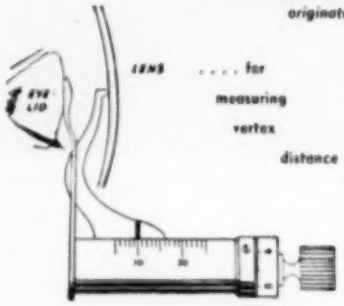

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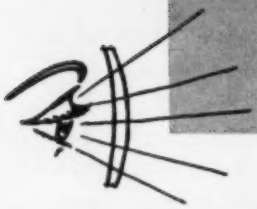

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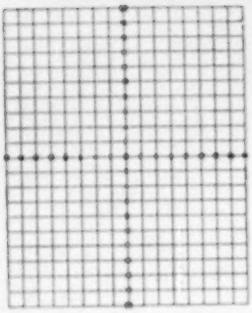

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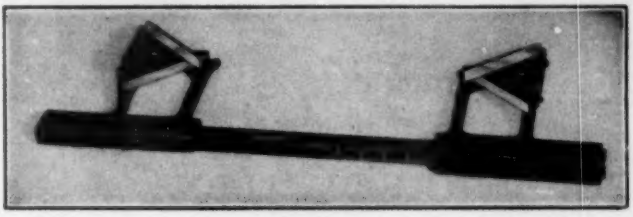

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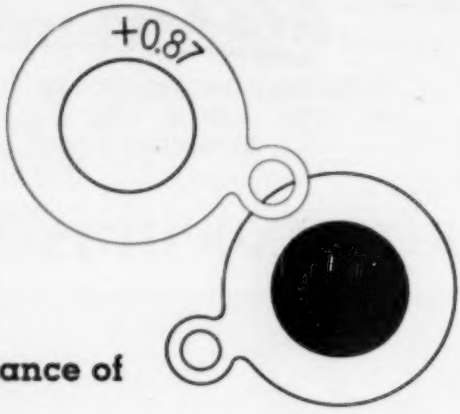

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1. Harrison, W. L.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas.

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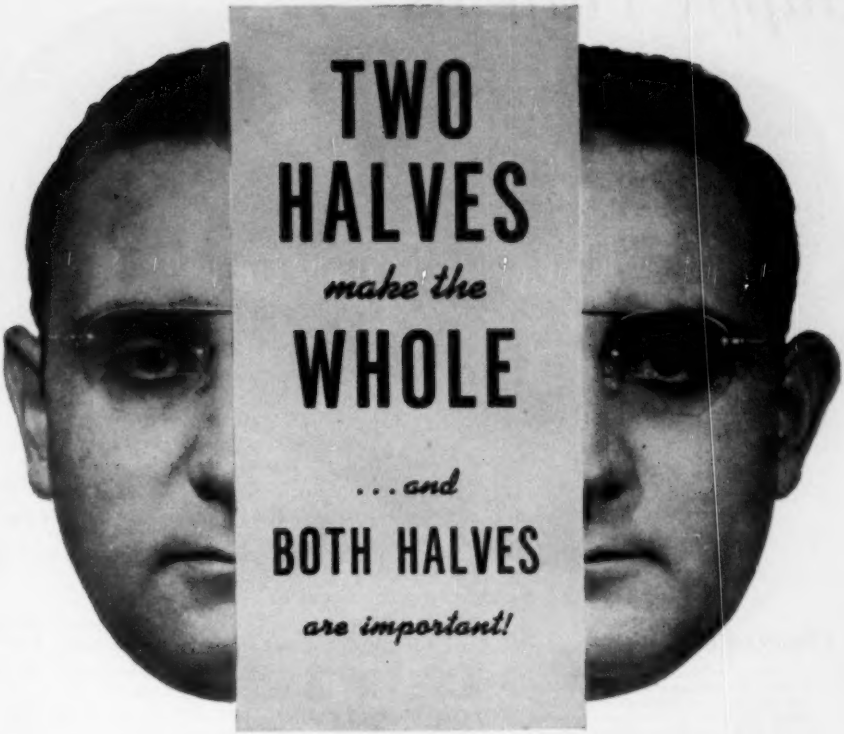

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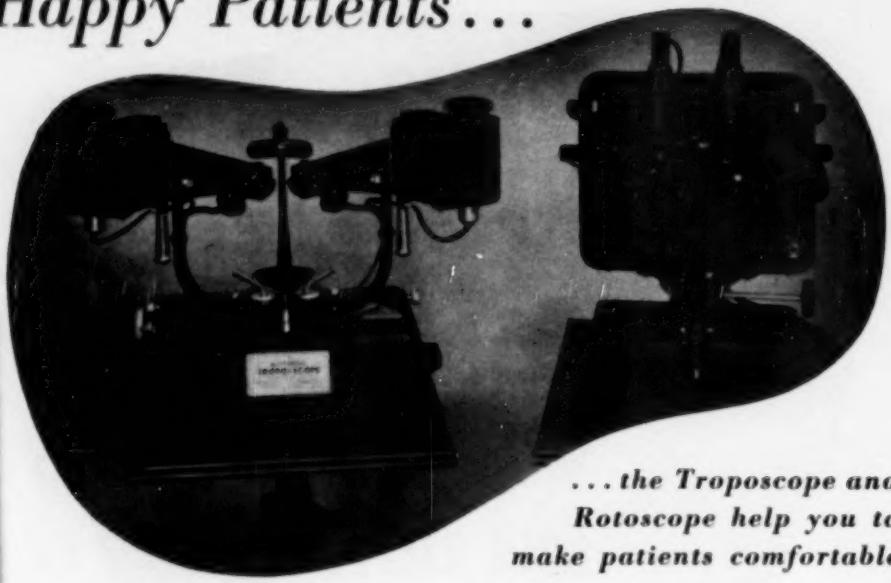

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 44 AUGUST 1950 NUMBER 2

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INCISION AND CLOSURE OF THE WOUND IN CATARACT OPERATIONS

A Study of the Graefe Knife Versus the Keratome-Scissors Incision and a Method of Suture of the Deep Wound

FREDERICK ALLISON DAVIS, M.D.

MADISON, WIS.

THE INCISION for cataract extraction has been a controversial subject since the immortal Daviel[1] first introduced his method of extraction, some two hundred years ago. It is generally conceded to be the most important step of the operation, and a successful outcome depends in large measure on the size, position and character of the initial opening and the skill with which it is made. In reviewing the history of the cataract operation one finds that innumerable methods of incision have been devised over the years in an effort to simplify and perfect the technic. In recent years new procedures have been introduced and older methods, long forgotten, have been revived by a new generation of ophthalmic surgeons. I have been interested in following these trends and have undertaken a study of some of them.

HISTORICAL REVIEW

Daviel's original incision was made in the cornea from below, just inside the limbal border, and included about one half of the corneal circumference. The initial opening was made with a lance-shaped knife, similar to the present keratome, and the wound was then enlarged with a double-edged knife and scissors. Thus, a very large "corneal flap" was effected, by which name the operation was known for more than one hundred years.

Soon after Daviel's corneal flap operation was introduced, corneal incisions were made in every conceivable position and manner, so that practically no part of the cornea was spared. New instruments, especially knives of varying sizes and shapes, were soon introduced to replace the more cumbersome keratome, knife and scissors of Daviel.

From the Department of Ophthalmology, University of Wisconsin Medical School.

Read before the New York Academy of Medicine, Section of Ophthalmology, March 21, 1950.

1. Daviel, J.: Sur une nouvelle methode de guerir la cataracte par l'extraction du cristalin, Mém. Acad. roy. de chir. **5**:369, 1753.

The poor results which followed these operations led von Graefe to abandon the corneal incision, and in 1853 he proposed a modified linear incision which was made in the sclera just above the upper border of the limbus, perfecting this with the early model of his well known knife. This incision proved to be too small and too peripheral, even though he subsequently enlarged it. Von Graefe's operation was popular for some time, but complications incident to the position and small size of the incision led to further modifications and a return by some surgeons to

Fig. 1 (from Daviel,[1] original plate XX).—*A*, cataract; *B*, keratome incision in the lower margin of the limbus; *C*, enlargement of the incision with double-edged knife; *D* and *E*, further enlargement of the incision with scissors, right-handed and left-handed models being used; *F*, *G* and *H*, reflection of the corneal flap and incision of the capsule with a knife needle; *I*, manual delivery of the lens by pressure on the lower half of the globe.

the larger corneal flap operation made with the knife, or the lance-shaped knife, such as Weber's. Incisions at the inferior border of the limbus were again advocated by leading surgeons of that day, but finally the incision came to rest, at least for a time, at the upper limbal border.

For the past fifty to sixty years a limbal incision, made with the von Graefe knife, has been rather generally accepted as the one of choice by

the great majority of ophthalmic surgeons, though a limited group particularly those who follow the Smith-India teaching, have retained the corneal incision.

Thus, the site and manner of making the incision have been subject to change ever since the inception of the operation. It has been a battle-ground which has been fought over, perhaps, with greater intensity than similar controversies concerning the extracapsular and intracapsular methods of extraction or the round pupil and complete iridectomy technics. With the recent revival of the so-called newer methods of making the incision, the battle seems destined to be resumed and refought for many generations to come.

RECENT MODIFICATIONS OF THE INCISION

Recently some surgeons have abandoned the classic limbus section made with the von Graefe knife and have reverted to a piecemeal type of incision made with angular knives, keratome and scissors.

Some operators consider these methods simpler and safer and attended with fewer postoperative complications. O'Brien,[2] McLean,[3] Atkinson,[4] Green,[5] Castroviejo[6] and others have advocated various modifications of these multiple incision types of operations. Claiborne[7] attempted to revive the keratome-scissors incision some forty years ago, and Beard[8] advocated the method in his textbook; but their teaching attracted few followers until the present revival of the method.

Some surgeons recommend incisions beneath a prepared conjunctival flap, while others make the incision directly in the cornea, relying on corneoscleral sutures for coaptation of the lips of the wound.

CLOSURE OF THE WOUND

Methods directed toward a more accurate closure of the cataract wound are of comparatively recent origin. Until recent years coaptation of the lips of the incision was left more or less to chance, and a speedy,

2. O'Brien, C. S.: Comparison of the Keratome-Scissors and Graefe Knife Incisions for Cataract Extractions, Am. J. Ophth. **26**:508, 1943.

3. McLean, J. M.: A New Corneoscleral Suture, Arch. Ophth. **23**:554 (March) 1940.

4. Atkinson, W. S.: Preliminary Report of Corneal Section with Long Bevel and Conjunctival Flap for Cataract Extraction, Tr. Am. Ophth. Soc. **43**:97, 1945.

5. Green, J.: An Eclectic Technic for Intracapsular Extraction of Cataract, South. M. J. **35**:1076, 1942.

6. Castroviejo, R.: Trends in Cataract Surgery, in Sorsby, A.: Modern Trends in Ophthalmology, ed. 2, New York, Paul B. Hoeber, Inc., 1947, vol. 2, pp. 449-468.

7. Claiborne, J. H.: Extraction of Cataract with a Lance-Shaped Knife, Tr. Am. Ophth. Soc. **11**:618, 1906-1908.

8. Beard, C. H.: Ophthalmic Surgery, ed. 2, Philadelphia, The Blakiston Company, 1914.

smooth healing of the corneal wound depended chiefly on the site and size of the incision, the precision with which it was made and the behavior of the patient after operation.

CONJUNCTIVAL FLAPS

The use of the conjunctival flap was the first important advance in the promotion of a prompter and firmer closure of the wound. The flap as first advocated was small and wholly inadequate to protect the deep wound. Its size and extent were gradually increased, so that it not only served to aid in prompter closure of the incision but added a definite factor of safety in the prevention of infection. Fashions in the conjunctival flap have run the gamut from a small, pointed tab of tissue to deep pocket flaps, which require extensive undermining of large areas of the conjunctiva. Delivery of the lens beneath a conjunctival bridge was practiced for a time. The sliding flap of Kuhnt and van Lint, which is drawn down and sutured over a limbus section, is still advocated by some leading surgeons. Like many other procedures, use of the conjunctival flap has perhaps been overdone. Considerable hemorrhage not infrequently accompanies extensive dissection of the flap. I have seen total subconjunctival suffusion of blood as a result of dissection of a pocket flap, much to the embarrassment and inconvenience of the operator. However, the advantages of a well made conjunctival flap of proper extent, width and thickness cannot be overemphasized. Primary adhesion of the flap to the underlying sclera aids in quickly sealing the wound, especially if it is well sutured. Its value in preventing infection and downgrowth of epithelium, likewise, cannot be too strongly stressed.

SUTURES

The first attempts at more accurate closure of the corneal wound in cataract operations by sutures are credited to Williams,[9] who in 1869 described a simple appositional silk suture which was inserted in the lips of the corneal wound. He later modified the suture and placed it in a small conjunctival flap. Mendoza[10] proposed a corneal suture in 1889. Kalt[11] began his work with suturing in 1894, but his simple corneoepiscleral overriding suture received little attention and was not adopted by many surgeons. Ellett,[12] however, was a warm advocate of this

9. Williams, H. W.: Arch. Ophth. & Otol. **1**:102, 1869.

10. Mendoza, S. de F.: Nouveaux faits de suture de la cornée dans l'extraction de la cataracte, Bull. et mém. Soc. franç. d'opht. **10**:63, 1892.

11. Kalt, E.: Corneal Suture in Cataract Extraction, Arch. Ophth. **23**:421, 1894.

12. Ellett, E. C.: The Use of the Suture in Cataract Extraction, in Contributions to Ophthalmic Science, edited by W. H. Crisp and W. C. Finnoff, Menasha, Wis., George Banta Publishing Company, 1926, p. 229.

suture and used it with satisfaction in a large series of operations. The use of sutures, especially conjunctival, has increased in popularity during the past twenty-five years, and more recently the corneoscleral suture, of various types, is being adopted by many operators. Many of the corneoscleral sutures are based on the original Kalt stitch, slight modifications having been suggested by Liegard,[13] Stevenson,[14] Stallard,[15] Higgins [16] and others.

The appositional type of suture is gaining in popularity, especially that devised by Verhoeff and by McLean. McLean's suture, which is quite similar to Lindner's,[17] is a true appositional suture, inserted in the lips of the wound so that the knot is tied outside the conjunctival flap. It affords accurate closure of the deep wound. It is preplaced in a prepared groove and therefore interferes somewhat with a full knife section. When two or more sutures are used, the multiplicity of threads makes it extremely difficult to avoid cutting them at times with the knife or scissors. Most authors prefer silk for sutures, but some surgeons, notably Hughes and associates,[18] and Alger,[19] have recommended surgical gut. I [20] published a preliminary report concerning a buried surgical gut stitch in the ARCHIVES in 1944. Innumerable methods of suturing the cataract incision will be found in the recent literature, but a review of these is beyond the scope of this paper.

Deep suturing adds to the complexity of the operation and consumes more time. If the sutures are truly deep—deep enough to be of real service—they are difficult to insert, especially with the imperfect needles now available. Much added trauma may be inflicted on the globe, unless extreme skill is exercised in inserting them. The Kalt-Liegard-Stallard type of suture is more easily inserted and removed, but closure of the wound is not so accurately or firmly effected. Immediate postoperative

13. Liegard, H.: Une modification au procédé de suture de la cornée dans l'operation de la cataracte, Ann. d'ocul. **149**:119, 1913.

14. Stevenson, cited by Beard,[8] p. 554.

15. Stallard, H. B.: A Corneo-Scleral Suture in Cataract Extraction: Its Technique and Advantages, Brit. J. Ophth. **22**:269, 1938.

16. Higgins, S.: Safest Cataract Operation with Reference to Astigmatism Following Corneal Conjunctival Suture, Illinois M. J. **62**:419, 1932.

17. Lindner, K.: Ueber Abänderungen der intrakapsulären Staroperation, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **52**:392, 1938.

18. Hughes, W. L.; Guy, L. P., and Romaine, H. H.: Absorbable Sutures in Cataract Surgery, Arch. Ophth. **32**:362 (Nov.) 1944.

19. Alger, L. J.: Use of Absorbable Corneoscleral Sutures in Cataract Surgery, Arch. Ophth. **38**:665 (Nov.) 1947.

20. Davis, F. A.: Catgut Sutures for Closure of the Deep Corneoscleral Wound in Operations for Cataract: A Preliminary Report, Arch. Ophth. **31**:321 (April) 1944.

reaction is increased in most cases in which deep suturing is employed, and it often persists until the sutures are removed. Removal of the deeply placed suture, especially of the McLean type, may prove difficult at times, even at the end of two weeks.

Akinesia will be found helpful, if not essential, in patients who are uncooperative or who have pronounced blepharospasm. Accidents, such as loss of or bleeding into the anterior chamber, may attend removal of the sutures. Hughes and Owens [21] directed attention to this hazard when they reported loss of chamber in 3 per cent and bleeding into the chamber in 3.6 per cent of the cases which they reviewed. They also found that deep sutures increased the incidence of wound infection.

My colleagues and I have continued our study of different types of suturing of the deep wound, and conclusions based on this study will be referred to later.

KERATOME-SCISSORS INCISION VERSUS GRAEFE KNIFE INCISION: A STATISTICAL COMPARISON OF THE TWO METHODS

The main purpose of this presentation is to report the results which we have obtained with the keratome-scissors incision and the knife incision in performing intracapsular cataract extraction. A series of 257 cases with the keratome-scissors incision will be compared with 202 cases with the Graefe knife incision. In all these cases deep sutures were employed. In addition, some of the complications which followed conjunctival suture in a previously reported series [22] of 500 intracapsular extractions will be noted for comparison.

The cases were consecutive and unselected, except that cases of cataract due to uveitis and of cataract occurring in eyes previously operated on for glaucoma were generally eliminated. The operations were performed by resident physicians and junior and senior staff members of the Wisconsin General Hospital.[23] The majority of the extractions were combined with iridectomy, the round pupil method being used in only 15 to 18 per cent of the two more recent series. Preliminary iridectomy was used in about 50 per cent of the series previously reported.

21. Hughes, W. F., Jr., and Owens, W. C.: Extraction of Senile Cataract, Tr. Am. Acad. Ophth. **49**:251, 1945; Am. J. Ophth. **28**:40, 1945; Postoperative Complications of Cataract Extraction, Tr. Sect. Ophth. A. M. A., 1946, p. 44.

22. Davis, F. A.: Personal Experiences with Intracapsular Cataract Extractions, Arch. Ophth. **19**:867 (June) 1938; Intracapsular Cataract Extraction: Statistical Survey of 500 Consecutive Cases, ibid. **31**:367 (May) 1944.

23. Included in the series of cases in which knife incision with deep suture was used were some private cases at the Madison General Hospital, in which operations were performed by senior members of our staff.

TECHNIC

Keratome-Scissors Incision.—A conjunctival flap, usually 4 to 5 mm. at its peak, tapered to the sides and joining the cornea in the horizontal meridian, was dissected with scissors. The keratome was then introduced at the limbus at 12 o'clock beneath the flap, the incision varying from 5 to 7 mm. The deep suture was then inserted, the loop drawn aside and the wound enlarged on either side with curved scissors of the Stevens type until it included about 40 to 50 per cent of the corneal circumference. Iridectomy was then performed, the lens extracted in capsule and the deep suture tied. The conjunctival flap was closed with six silk sutures. Three types of deep sutures were used: (1) a buried 00000 plain surgical gut appositional stitch, previously reported;[20] (2) the McLean silk suture, and (3) two corneoepiscleral-conjunctival silk sutures, similar to the stitch in use at one time at the Institute of Ophthalmology of the Presbyterian Hospital.

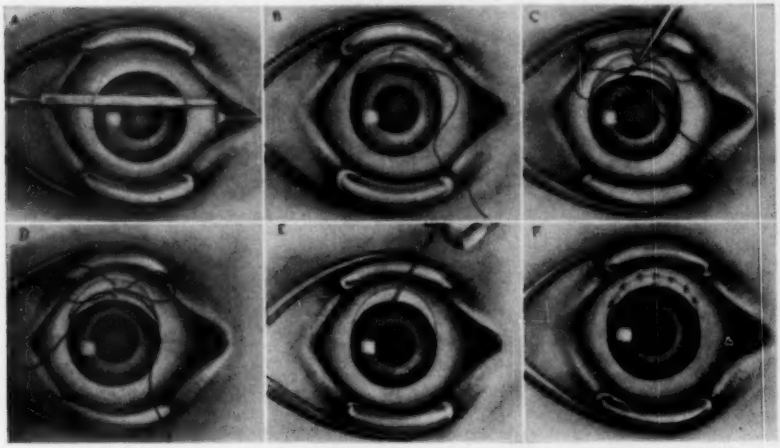

Fig. 2.—My method of incision and wound closure. (*A*) The limbus incision (40 per cent) is made with the Graefe knife, ending with a complete conjunctival flap. (*B*) Atraumatic® needle attached to 000000 braided silk suture is introduced into the cornea at the base of the flap. (*C*) The needle is then reinserted through the edge of the scleral lip of the wound. (*D*) The needle is then reversed and brought out through the conjunctiva at the base of the conjunctival flap immediately above the corneal puncture. (*E*) The lens has been delivered and the wound closed by drawing up the ends of the suture. (*F*) The deep suture is tied, and six or more additional sutures are inserted, which close the conjunctival incision.

Knife Incision.—In 202 cases in which the knife was used, the incision was made with a moderately narrow Graefe knife and usually included about 40 per cent of the corneal circumference. A limbal incision was attempted of sufficient depth to permit a conjunctival flap throughout the section. In some cases in which the knife incision was considered too small a slight enlargement was made at one, and at times both, ends of the wound with scissors. In 151 operations the knife alone was used, and in 51 cases the wound was slightly enlarged with scissors. After the full knife section, one of two appositional corneoscleral silk sutures were inserted in a manner shown in figures 2 and 3 (two sutures being used in 75 operations and

one suture in 127 operations). The rest of the technic was identical with that used with the keratome-scissors incision. In the 500 cases of knife section with conjunctival sutures only, the procedure was the same as that shown in figures 2 and 3 except that the deep stitch was not used.

Present Method of Closure of the Wound (figs. 2 and 3).—The deep suture which I have used during the past three years is illustrated in figures 2 and 3. I have called it a reverse McLean stitch, since in the end the wound closure is almost identical with that with the McLean suture. I have found this method of suturing very satisfactory in some 300 operations in which it has been used.

The method of insertion differs somewhat from that described by McLean. The suture is not preplaced, nor do I use a prepared groove.

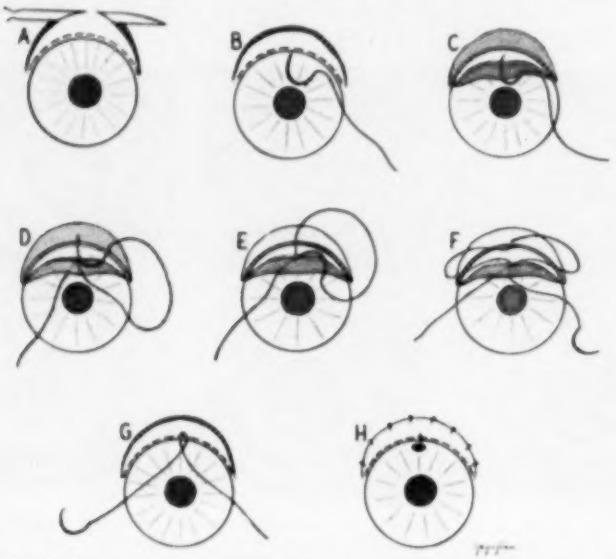

Fig. 3.—Diagrammatic illustration of method of incision and insertion of the deep and conjunctival sutures, as shown in figure 2. *A*, limbus incision (40 per cent) with Graefe knife, ending with a complete conjunctival flap; *B* and *C*, atraumatic needle attached to 00000 braided silk suture, introduced into cornea at base of flap; *D*, needle reinserted through edge of scleral lip of wound; *E* and *F*, needle reversed and brought out through conjunctiva at base of conjunctival flap immediately above corneal puncture; *G*, lens delivered and wound closed by drawing up the ends of the suture. *H*, deep suture tied and six or more additional sutures inserted, closing the conjunctival incision. The needle does not puncture the entire thickness of the cornea but engages the outer half only. The edge of the scleral wound is likewise split by the needle, so that the suture lies outside the chamber angle. Loss of the chamber, or bleeding into it on removal of the suture, is thereby avoided.

A limbal section is made with the Graefe knife. When the knife completes the corneoscleral incision, it is continued upward to include a liberal conjunctival flap. The needle is inserted into the cornea at 12 o'clock, just below the base of the flap,

and it is then reinserted in the edge of the scleral wound, after which the needle is reversed and brought out through the conjunctiva at the base of the flap, immediately above and close to the original corneal puncture. The thread is then drawn out of the deep incision, which it bridges, the loop being of sufficient size to allow ample space for delivery of the lens. The operation proceeds in the usual manner. After delivery of the lens, the loop is drawn up and the suture tied. The toilet of the wound is completed after tying the suture, and at the completion of the operation six or more interrupted sutures are used to close the conjunctival incision. The deep suture is usually not removed before the twelfth or thirteenth postoperative day. The conjunctival sutures are usually removed about the tenth day. Two or more deep sutures are used at times, especially when the round pupil technic is employed.

COMPLICATIONS

Loss of Vitreous.—Vitreous presented or was lost in 9.7 per cent of the cases with the keratome-scissors incision, in 7.0 per cent of the cases with the knife incision–deep suture technic, and in 7.2 per cent of the

TABLE 1.—*Complications Following Intracapsular Cataract Extraction: A Comparison of Different Methods of Incision and Closure**

Complications	Keratome-Scissors Section with Deep Suture	Knife Section with Deep Sutures	Knife Section with Conjunctival Sutures
No. of operations	207	202	500
Loss of vitreous	(35) 9.7%	(14) 7.0%	(36) 7.2%
Prolapse of iris	(1) 0.4%	(1) 0.5%	(7) 1.4%
Iridocyclitis	(25) 9.7%	(8) 4.0%	(15) 3.0%
Hemorrhage in anterior chamber	(56) 21.8%	(14) 7.0%	(46) 9.2%
Retinal detachment	(5) 2.0%	(2) 1.0%	(3) 0.4%
Secondary glaucoma	(17) 6.6%	(3) 1.5%	(4) 0.8%

* The statistical analysis was based on Pearson's X^2 square method. No factor has been regarded as of statistical significance unless the probability of chance or error was less than 1 in 20 ($p = 0.05$ per cent).

earlier series with knife incision and conjunctival sutures only. Statistical analysis shows no significant relation of the incidence of loss of vitreous to the type of incision made, the suture used or the iridectomy employed. Vitreous presented most frequently after delivery of the lens, except in cases of liquid vitreous or subluxated lens, when loss followed the incision. Severe loss of vitreous was rare, owing no doubt to present day methods of anesthesia and suturing, and poor vision resulting from this complication was equally uncommon. In about 70 per cent of the cases in which vitreous was lost visual acuity of 20/30 or better was attained. While these results are surprisingly good, I agree with Knapp [24] that loss of vitreous is a complication never to be minimized and always to be regarded with apprehension.

24. Knapp, A.: The Complications of the Forceps Intracapsular Cataract Operation, Based on an Analysis of 500 Successive Cases, Tr. Am. Ophth. Soc. **34**: 162, 1936.

Prolapse of Iris.—Prolapse of the iris occurred in 1 case in each of the two series in which deep sutures were used and in 7 of the 500 operations in which conjunctival sutures only were employed. In one-half the latter cases prolapse developed after round pupil extraction. The incidence of prolapse of the iris was too small for statistical comparison of the series with conjunctival sutures and the series with deep sutures, but it is my clinical impression that deep sutures are of great value in the prevention of prolapse of the iris, especially with the round pupil technic. Adhesion of the pillars of the iris to the wound occurred in 14 cases after the keratome-scissors incision and in 5 cases after the knife incision. In some of these cases the adhesion appeared to be the cause of a filtering bleb.

IRIDOCYCLITIS

Iridocyclitis developed in 9.7 per cent of cases with keratome-scissors incision, in 4 per cent of cases in which the knife incision and deep sutures were employed and in 3 per cent of the series in which the knife incision and conjunctival sutures were used. There was little difference in the frequency of this complication in the two series with knife incisions, but the incidence was significantly higher after the keratome-scissors operation. In some cases iridocyclitis followed hyphema, loss of vitreous, delayed restoration of the anterior chamber, late rupture of the hyaloid membrane or low grade infection, and in others no cause was found. We attributed the lower incidence of this complication with the Graefe knife incision to minimal trauma and superior wound healing. Mild injection of the globe was observed in many cases, persisting in some instances until absorption or removal of the deep sutures. This complication was not related to the type of deep suture used.

Hyphema.—Postoperative hyphema followed the keratome-scissors incision in 21.8 per cent of cases. This is significantly higher than the incidence of this complication in the two series with knife incisions, viz., 7.0 and 9.2 per cent, respectively, for the deep suture series and the conjunctival suture series. About 25 per cent of all hemorrhages in the anterior chamber were attributed to trauma, and in 75 per cent of the cases of hemorrhage no history of trauma was obtained; many hemorrhages were small and absorbed in a few days. Hyphema which invaded the vitreous was the cause of serious visual loss in 2 cases in the conjunctival suture series, in which it was associated with severe postoperative trauma, and may have been a contributing factor in 3 cases of secondary glaucoma in the keratome-scissors incision series; with these exceptions, however, hemorrhage in the anterior chamber was usually more annoying than serious. Our data show no significant relation of this complication to the type or number

of deep sutures used. Bleeding occurred most commonly about the sixth postoperative day and, except in cases in which it was severe, was rarely associated with loss of the anterior chamber.

Retinal Detachment.—The incidence of retinal detachment after keratome-scissors incisions was somewhat higher than average, being 2.0 per cent, but showed no significant variation from that encountered after knife incisions with superficial or with deep sutures. Duehr,[25] in a survey of retinal detachments in the eye department of the Wisconsin General Hospital, found that 16 cases of retinal detachment developed in a series of 1,750 extractions, an incidence of 0.9 per cent.

Secondary Glaucoma.—The incidence of secondary glaucoma showed a significant increase after the keratome-scissors incision as compared with that in operations performed with the knife incision. It developed in 6.6 per cent of cases with the keratome-scissors incision and in 1.5 and 0.8 per cent of cases with knife incisions and deep and conjunctival sutures, respectively.

Of the 17 cases which followed the keratome-scissors technic, the glaucoma was associated with delayed reformation of the chamber in 10 and with iridocyclitis in 5, and in 2 cases nothing of significance was found. In the 10 cases in which the glaucoma was attributed to a leaky wound, reformation of the chamber was delayed from the eighth to the twenty-second postoperative day. Detachment of the choroid was present in 6 of these 10 cases. Anterior synechias were demonstrated by the slit lamp or gonioscope in 5 of the cases. In the remainder data were insufficient for definite conclusions. Glaucoma was noted usually from one to three months after operation in most of these cases, but in 2 it occurred one and one-half and four years later, respectively. In these 2 cases the late closure may be of questionable significance. In 4 of the 10 cases of glaucoma attributed to delayed reformation of the chamber the tension was satisfactorily controlled by cyclodialysis, with vision of 20/20 or better. In the other 6 cases the tension was controlled by miotics, 20/30 vision being maintained in 5 cases and 20/50 vision in 1 case, but in 2 cases vision was later lost as a result of retinal detachment. Of the cases of glaucoma attributed to iridocyclitis, visual results following operation or treatment were poor in all but 1 case. In other words, operation and miotics were successful in the cases in which anterior synechias were the probable cause of the glaucoma but were not successful in cases in which it was due to iridocyclitis.

Of 202 cases of knife incisions with deep sutures, glaucoma developed in only 3 cases. In all these restoration of the chamber was delayed from the eighth to the twenty-first day. In 2 of the cases the glaucoma was

25. Duehr, P. A.: Some Primary Considerations in Retinal Detachment, Wisconsin M. J. (May) 1947.

apparently due to this delayed restoration, although contact of the hyaloid membrane with the cornea for some time may have been a factor in 1 case. An acute rise in tension in 1 case was produced by strangulation of a knuckle of vitreous by a round pupil. In 2 of the cases the tension was very well controlled by surgical measures and in 1 reasonably well by miotics.

Statistical analysis shows that the lower incidence of secondary glaucoma in the previously reported series of extractions by the knife incision–conjunctival suture technic is not significantly different from that observed in the series of 202 cases in which the knife incision and deep suture technic was used.

Delayed Restoration and Late Loss of the Anterior Chamber.—Delayed restoration of the anterior chamber after the fourth post-

TABLE 2.—*Significant Differences in Wound Closure and Related Complications Following Knife and Keratome-Scissors Incisions*

Complications	Keratome-Scissors Incision with Deep Sutures	Knife Incision with Deep Sutures
No. of operations	257	202
Delayed restoration of anterior chamber (after 7th day)	(32) 12.5%	(7) 3.5%
Late loss of the anterior chamber	(30) 11.8%	(9) 4.5%
Incomplete wound closure		
Wound gape	(9) 3.5%	(1) 0.5%
Filtering bleb	(10) 3.7%	(6) 2.9%
Total	(19) 7.2%	(7) 3.4%
Secondary glaucoma associated with delayed restoration of anterior chamber	(10) 3.7%	(3) 1.4%
Choroidal detachments	(47) 18.3%	(5) 2.4%

operative day (the day of the first dressing, as a rule) occurred in 52 cases (20.2 per cent) of the keratome-scissors operation and in 28 (13.8 per cent) of the knife–deep suture operation. When the statistics were computed for restoration after the fifth day, the ratio changed substantially, the series with the keratome-scissors incision still showing delayed restoration in 47 cases (18.3 per cent) and the series with the knife incision–deep suture operation in 17 cases (8.4 per cent).

A further variation in closure of the incision with the two methods used was noted after the seventh postoperative day, when the chamber remained partly restored or flat in 32 cases (12.5 per cent) after the keratome-scissors operation and in only 7 cases (3.5 per cent) after the knife operation. All cases were recorded as showing "delayed restoration" until the chamber had regained the full depth usually noted after cataract extraction.

Late loss of the chamber showed a comparable difference in the firmness of wound closure, since such a loss followed the keratome-

scissors incision in 30 cases (11.6 per cent) and the knife incision in 9 cases (4.5 per cent).

These differences are highly significant, indicating more rapid and more effective closure of the wound in our cases after the knife incision. The method of deep suturing employed in this series of cases with knife incisions may also be a factor, but the same suture (McLean) was less effective when used with the keratome-scissors incision (table 8).

Insufficient data were available for an evaluation of delayed restoration of the chamber in the earlier series of cases, of knife incisions with conjunctival sutures only.

As previously stated, secondary glaucoma developed after the keratome-scissors incision in 10 cases and after the knife incision in 3 cases, in all of which there was delayed restoration of the chamber. The fact that in all these cases glaucoma followed delayed restoration, and that it did not occur in any of the cases with late loss of the chamber may be explained by the difference in the time the chamber was shallow—the average for delayed restoration being thirteen days and the average for late loss of chamber seven days.

Incomplete Closure of the Wound.—The incidence of incomplete closure of the wound, as evidenced by gaping of the wound or a filtering cicatrix, was significantly higher after the keratome-scissors incisions. It occurred in 19 cases of the keratome-scissors operation and in 7 cases after the knife incision with deep suture.

In the series with the keratome-scissors incision, actual visible separation of the deep wound occurred in 9 cases and a fistulizing scar in 10 cases. Of the 9 cases, gaping was slight in 6 and fairly wide in 3, in 2 of which resuturing of the wound was required. Serious loss of vision followed the latter. Six of the 7 cases of incomplete closure which developed after the knife incision were cases in which a small filtering bleb developed at one point in the incision. Except for these, there was only 1 case in which a slight separation or spreading of the wound followed the knife incision–deep suture operations.

The fistulizing scar which developed after both methods of operation did not seriously interfere with the final result in any of the cases. In 6 of the 16 cases the filtration occurred at the site of an adherent iris pillar, indicating that this was probably the source of the leak, as has recently been shown by Dunnington.[26]

Slight separation of the lips of the deep wound beneath the conjunctival flap occurred in a number of the earlier series of cases of knife incisions, in which conjunctival sutures only were employed. The presence of an adequate conjunctival flap, well sutured, was of immense

26. Dunnington, J. H.: Healing of the Cataract Incision, Gifford Lecture, Chicago Ophthalmological Society, January 1950, to be published.

help in preventing actual rupture of the wound in most of these cases, and firm closure of the deep wound eventually developed in most of them.

Choroidal Detachment.—Another troublesome complication which followed the keratome-scissors incision was choroidal detachment, occurring in 47 cases, while in only 5 cases were detachments observed to follow the knife incision–deep suture procedure. Delayed restoration or late loss of the chamber was present in 46 of the combined total of 52 cases of choroidal detachment, detachments (small) with a normal chamber being observed in only 6 cases. However, not all shallow chambers were associated with choroidal detachment, a considerable number showing no detachment. Of a total of 62 cases recorded in which there was delayed restoration of the chamber, choroidal detachment occurred in 40, while in 22 cases no detachment could be demonstrated.

If the healing is uncomplicated I do not examine the fundus with the ophthalmoscope until the tenth to the fourteenth postoperative day; so many small detachments may not have been observed. While choroidal separation presumably occurs with great frequency after cataract extraction and is regarded as a minor complication by some authors, it proved otherwise in several cases of the keratome-scissors operation. Of 5 cases in which the detachment was extensive and prolonged, acuity below 20/70 resulted in 4, and there was total loss of vision in 1 case. Pigment streaks and folds in the retina were observed in 2 cases, and macular edema was noted in 2 cases. The great increase in number of choroidal detachments which followed the keratome-scissors incision suggests that trauma incident to this type of incision may be an important factor in its production.

Relation of Complications to Types of Deep Sutures (tables 3 and 4).—Analysis of the complications which developed in the keratome-scissors operations with relation to the type of suture used shows that the corneoepiscleral-conjunctival suture was definitely inferior to both the surgical gut and the McLean suture. Delayed restoration or late loss of the chamber occurred in 48.5 per cent of the cases in which two corneoepiscleral-conjunctival stitches were used and in only 14.5 and 15.8 per cent, respectively, in which the McLean stitch and buried surgical gut suture were employed. Choroidal detachments were more frequent after the corneoepiscleral-conjunctival suture than with either of the other two methods. Secondary glaucoma occurred too infrequently for statistical analysis but followed the same trend observed in the other complications related to wound closure.

Epithelial Downgrowth.—Our experience with epithelial downgrowth is represented by 7 cases, in only 1 of which it followed intra-

TABLE 3.—*Relation of Complications in Series of Keratome-Scissors Incisions to Suture Used**

Complications	Corneoscleral-Conjunctival Suture	McLean Suture	Buried Surgical Gut Suture
No. of cases	64	54	139
Delayed restoration (after 7th day) and late loss of anterior chamber (total 62)	(32) 48.3%	(8) 14.8%	(22) 15.8%
Choroidal detachments (total 47)	(19) 29.6%	(7) 13.0%	(21) 15.1%
Secondary glaucoma (total 17)	(8) 12.5%	(2) 3.7%	(7) 5.0%
Adherent pillars	(6) 9.3%	(1) 1.8%	(7) 5.0%

* This table shows how the stitch may affect the results when the incision was the same in all cases.

The corneoscleral-conjunctival stitch, as used in these cases, no doubt contributed to the faulty wound closure, possibly owing to overriding of the corneal lip of the wound. The stitch was not appositional. The scleral bite was inserted before or after the incision, parallel to the incision near the edge, and the corneal bite was radial, at the base of the flap. This apparently lifted the corneal lip of the wound up over the scleral lip, if the suture was tied tightly. Moreover, the conjunctival flap was somewhat narrower and covered the wound less effectively than the flap used with the buried surgical gut and McLean sutures. I have noted the same defect in the overriding stitch of the Kalt-Liegard-Stallard type in some of a limited number of cases in which it was tried.

TABLE 4.—*Complications Following Use of Different Types of Deep Sutures After Keratome-Scissors Incision and Intracapsular Cataract Extraction*

Complications	Keratome-Scissors Incision	Buried Surgical Gut Suture	McLean Suture	Corneo-scleral-Con-junctival Suture
No. of operations	207	139	54	64
Loss of vitreous	(25) 9.7%	10.0%	11.1%	7.9%
Prolapse of iris	(1) 0.4%	0	0	1.6%
Iridocyclitis	(25) 9.7%	8.6%	13.0%	9.4%
Hemorrhage in anterior chamber	(56) 21.8%	23.0%	22.0%	21.9%
Delayed anterior chamber formation (after 7th day)	(32) 12.5%	5.8%	7.4%	31.3%
Late loss of A. C.				
With choroidal detachment	(16) 6.2%	5.0%	3.7%	10.9%
No choroidal detachment	(14) 5.4%	5.0%	5.5%	6.3%
Total	(30) 11.6%	10.0%	9.3%	17.2%
Choroidal detachment with normal anterior chamber	(6) 2.3%	2.2%	1.9%	3.1%
Total number of choroidal detachments	(47) 18.3%	13.1%	13.0%	20.6%
Retinal detachment	(5) 2.0%	2.2%	1.9%	1.6%
Secondary glaucoma	(17) 6.6%	5.0%	3.7%	12.5%
Corneal haziness (striate keratitis over 2 wk.)	(15) 5.8%	3.6%	7.4%	9.4%
Vitreous opacities impairing vision	(8) 3.1%	2.2%	1.9%	6.2%
Incomplete wound closure				
Wound gape	(9) 3.5%	3.6%	3.7%	3.1%
Filtering bleb	(10) 3.9%	3.6%	3.7%	4.7%
Total	(19) 7.4%	7.2%	7.4%	7.8%
Infection around suture	(4) 1.6%	(3) 2.2%	(1) 2%	0
Adherent pillars	(34) 5.4%	(7) 5%	(1) 1.8%	(6) 9.3%

capsular extraction. In this case, one of the series used in this report, it developed after a keratome-scissors incision. In the other 6 cases, 2 of our own, and 4 referred by colleagues, it followed extracapsular extractions. In 5 of these cases scissors were used in the incision. In 1 case an epithelial cyst was successfully destroyed by aspiration and injection of 3 per cent tincture of iodine. On the basis of these 7 cases, in 6 of which there was microscopic confirmation, it is my impression that downgrowth is more likely to occur after extracapsular extraction in which cortical remains or capsule is present. The type of incision, especially the use of scissors for enlargement of a keratome or knife incision, may also be a factor. Implantation of epithelium could be caused by the crushing effect of the scissors if no flap were used. This apparently occurred in 1 case of the series used for this report and in another case which has been observed since this paper was prepared. The imper-

TABLE 5.—*Relation of Incision and Wound Closure to Final Vision and Average Astigmatism After Cataract Extraction*

Vision	Keratome-Scissors and Deep Sutures	Knife Section and Deep Sutures	Knife section and Conjunctival Sutures
No. of operations	257	202	500
20/15-20/30	73.6%	78.7%	82.6%
20/40-20/200	16.6%	16.7%	14.2%
Less than 20/200	5.3%	0.9%	2.2%
Patient did not return	4.5%	3.7%	1.0%
Average astigmatism	1.80 D.	1.80 D.	2.12 D.
20/40 or less due to operative complication	13.5%	8.4%	3.0%

fect apposition of the wound which follows an incision in which scissors are used extensively may invite downgrowth from the conjunctiva if the deep wound is inadequately covered. Poor healing and subsequent separation of the wound unquestionably predispose to epithelial inlay. The relative rarity of this complication in our experience we attribute to the use of a complete conjunctival flap adequately sutured.

Subchoroidal Hemorrhage.—This rare, though most serious, complication was encountered in 3 of the total of 959 cases here reviewed, all 3 occurring in the keratome-scissors series. In 1 case the globe was saved with a small measure of vision by prompt use of posterior sclerotomy and evacuation of the blood. This interesting case was recently reported by two members of our staff, Dr. P. A. Duehr and Dr. C. D. Hogenson.

Endophthalmitis and Suture Infection.—In 1 case in the keratome-scissors series the eye was lost from acute purulent endophthalmitis. Mild infection occurred at the site of the suture in 4 cases.

Visual Results (table 5).—Visual results following the keratome-scissors series of operations were surprisingly good considering the

higher incidence of most complications encountered. Vision of 20/30 or better was obtained in approximately 73.6 per cent of these cases, as compared with 78.6 and 82.6 per cent for the series of extractions using the knife incision. The higher percentage of poor results, vision of 20/40 or less, attributed to operative complications was noted after the keratome-scissors technic.

Astigmatism.—Average astigmatism was 1.93 D. with the keratome-scissors technic, 1.80 D. with the knife incision and deep sutures and 2.13 D. with the knife incision and conjunctival sutures only. It would appear, therefore, that reduction of postoperative astigmatism which follows the keratome-scissors technic is due to the use of deep sutures rather than to the method of incision. The incision, however, can be a definite factor in the amount of astigmatism, especially if it is placed too far forward in the cornea, as is noted at times with a poor knife section.

COMMENT

The chief claims advanced for the keratome-scissors incision are the alleged simplicity of the procedure, especially for the occasional operator, the beginner and the surgeon who fears the knife incision.

No doubt the operation may be approached with less "fear and trembling" than that which may at times attend the full knife incision. However, the keratome-scissors incision is by no means foolproof, and may be difficult at times if there is a strong thrust of vitreous, thereby leaving little room in the angle for the scissors. The wound in the end may be far from perfect as compared with that following a well performed knife section, when this is feasible. It is obvious that a perfect incision is difficult to obtain when more than one instrument is used, since it is virtually impossible to be sure that the keratome incision and the lateral incision which is made with the scissors are in perfect alinement. Furthermore, scissors are seldom as sharp as a knife, and not infrequently the tissues may buckle because the incision is made with an imperfect instrument.

An eye operated on by the keratome-scissors technic is shown in figure 4.

The left eye of a patient aged 82 was enucleated six weeks after an uncomplicated intracapsular cataract extraction with keratome-scissors incision. The incision was closed with one McLean stitch and six conjunctival sutures. A severe keratoiritis, probably due to low grade infection, developed immediately after operation and resisted all treatment.

There was delayed restoration of the anterior chamber until the eleventh post-operative day, but there was at no time any visible separation or spreading of the deep wound.

Fig. 4.—Sagittal section of an eye illustrating poor apposition and healing of the incision following a keratome-scissors incision for intracapsular extraction. In this figure, *ad* indicates adhesion of intact hyaloid membrane to incision, due to leakage of the wound; *c*, cornea; *cf*, conjunctional flap completely covering the deep incision; *cs*, receding choroidal separation; *csi*, overlapping of corneoscleral incision after use of scissors; *fi*, blocking of filtration angle from adherent root of the iris; *hy*, hyaloid membrane.

The eye, which was removed six years ago, was sectioned serially several differential staining methods being used.

Study of the sections showed fair approximation and healing of the wound in part of the incision, but as the medial side of the incision was approached, where enlargement with scissors had been made, there was overlapping of the lips of the corneal wound. Adhesion of the intact hyaloid membrane to the wound was noted at one point, where leakage had occurred. There were a receding separation of the choroid and almost complete occlusion of the angle of the chamber, due to adhesion of the iris to the posterior surface of the cornea and to the hyaloid membrane. However, elevation of intraocular pressure had not developed up to the time of enucleation, the tension being 10 mm. (Schiøtz).

The section (sagittal) shown was stained with Masson's trichrome method.

There were evidence of severe iritis, a small encapsulated focus of infection on the thickened hyaloid membrane and senile changes in various structures. The cornea, being thin, collapsed on fixation.

I believe the trauma produced by the extensive use of scissors is the main contributing factor in delayed wound closure, subsequent leakage and the various complications which may follow this.

The great increase in the number of choroidal detachments which followed the keratome-scissors operation raises the question of the cause of this complication. The current views that choroidal separation arises from transudation of fluid from the choroidal veins into the suprachoroidea due to sudden hypotony which follows the incision with a subsequent leaky wound seems plausible in some cases, especially those in which the detachment occurs at the time of or immediately after operation. Most of the latter are small, flat and of short duration. However, in the very large, trilobed detachments, some of which develop with coincident late loss of the chamber, a different origin seems likely. In many cases of this type the deep wound appeared well sealed, and in most instances no sign of leakage could be found. It would appear likely that the aqueous must escape backward into the suprachoroidal space by way of a tear or rent in the attachment of the ciliary body to the scleral spur, as originally postulated by Hofrat Fuchs.

Recent observations of Csillag,[27] of Budapest, tend to confirm this view. Csillag stated that the incidence of choroidal detachment was greatly increased after the deep scleral flap incision of Horvath's cataract operation. Additional confirmation of the influence of the incision was furnished by Waldstein,[28] who reported a marked increase of choroidal detachment following Czermak's pocket flap incision, which is made almost entirely with scissors. Another interesting observation brought

27. Csillag, F.: Early Post-Operative Detachment of the Choroid, Brit. J. Ophth. **33**:694, 1949.

28. Waldstein, Ernst, in discussion on Smith, J. W.: Recurrent Detachment of the Choroid Following Trephining Operations, Am. J. Ophth. **29**:466, 1946.

TABLE 6.—*Complications Following Knife Incision with Deep Sutures and Intracapsular Cataract Extraction*

Complications	Total	Knife Incision Alone	Knife-Scissors Incision
No. of operations	202	151	51
Loss of vitreous	(14) 7.0%	(11) 7.3%	(3) 5.9%
Prolapse of iris	(1) 0.5%	(1) 0.7%	(0) 0
Adherent pillars	(5) 2.5%	(4) 2.6%	(1) 2.0%
Iridocyclitis	(8) 4.0%	(5) 3.3%	(3) 5.9%
Hemorrhage in A. C.	(14) 7.0%	(11) 7.3%	(3) 5.9%
Delayed restoration of A. C. after 7th day			
With choroidal detachment (1)	(7) 3.5%	(4) 2.6%	(3) 5.9%
No choroidal detachment (6)			
Late loss of A. C.			
With choroidal detachment (4)	(9) 4.5%	(6) 4.0%	(3) 5.9%
No choroidal detachment (5)			
Total number of choroidal detachments			
With delayed closure (1)	(5) 2.5%	(2) 1.3%	(3) 5.9%
With late loss of anterior chamber (4)			
Retinal detachment	(2) 1.0%	(1) 0.7%	(1) 2.0%
Secondary glaucoma	(3) 1.5%	(2) 1.3%	(1) 2.0%
Incomplete wound closure	(6) 3.0%	(3) 2.0%	(3) 5.9%
Filtering cicatrix			

TABLE 7.—*Relation of Complications to Type of Incision*

Complications	Keratome-Scissors Incision	Total Knife and Knife-Scissors Incision	Knife Incision Alone	Knife-Scissors Incision
No. of cases	257	202	151	51
Loss of vitreous	(25) 9.7%	(14) 7.0%	(11) 7.3%	(3) 5.9%
Prolapse of iris	(1) 0.4%	(1) 0.5%	(1) 0.7%	(0) 0
Adherent pillars	(14) 5.4%	(5) 2.5%	(4) 2.6%	(1) 2.0%
Iridocyclitis	(25) 9.7%	(8) 4.0%	(5) 3.3%	(3) 5.9%
Hemorrhage in A. C.				
With trauma	(11) 4.3%	(5) 2.5%	(4) 2.6%	(1)
No trauma	(46) 17.9%	(9) 4.5%	(7) 4.6%	(2)
Total	(56) 21.8%	(14) 7.0%	(11) 7.3%	(3) 5.9%
Delayed restoration of A. C. after 4th day	(58) 30.2%	(39) 13.8%		
Delayed restoration of A. C. after 5th day	(47) 18.3%	(17) 8.4%		
Delayed A. C. (later than 7th day)				
With choroidal detachment	(20) 7.8%	(1) 0.5%		
No choroidal detachment	(12) 4.7%	(6) 3.0%		
Total	(32) 12.5%	(7) 3.5%	(4) 2.6%	(3) 5.9%
Late loss of A. C.				
With choroidal detachment	(16) 6.2%	(4) 2.0%		
No choroidal detachment	(14) 5.4%	(5) 2.5%		
Total	(30) 11.6%	(9) 4.5%	(6) 4.0%	(3) 5.9%
Incomplete wound closure				
Wound gape	(9) 3.5%	0	0	0
Filtering bleb	(10) 3.9%	(6) 3.0%	(3) 2.0%	(3) 5.9%
Total	(19) 7.4%	(6) 3.0%	(3) 2.0%	(3) 5.9%
Choroidal detachment with closure before 8th day	(3) 2.0%			
Choroidal detachment with normal A. C.	(6) 2.3%			
Total	(11) 4.3%	0	0	0
Total choroidal detachment	(47) 18.3%	(5) 2.5%	(2) 1.3%	(3) 5.9%
Retinal detachment	(5) 2.0%	(2) 1.0%	(1) 0.7%	(1) 2.0%
Secondary glaucoma	(17) 6.6%	(3) 1.5%	(2) 1.3%	(1) 2.0%
Subchoroidal hemorrhage	(2)	(0)	(0)	(0)
Epithelial downgrowth	(1)	(0)	(0)	(0)
Endophthalmitis	(1)	(0)	(0)	(0)

out by my study was the absence of choroidal detachment in cases in which vitreous was lost at operation, even when liquid vitreous flowed out and the eye partly collapsed. The significance of this is not clear, but it does indicate that sudden or profound hypotony cannot be the sole cause of all choroidal detachments.

Closure of the deep wound by sutures appears to mark a definite advance in the cataract operation. However, the innumerable methods suggested in the recent literature indicate that no standard procedure, satisfactory to all, has yet been developed. Some types of deep sutures, in my opinion, may be worse than none. A silk suture, based on the

TABLE 8.—*Complications Following Keratome-Scissors and Knife Incision with McLean Deep Sutures in Cases of Intracapsular Cataract Extraction**

Complications	Knife-Scissors Incision	Keratome-Scissors Incision
Number of operations	51	54
Loss of vitreous	(3) 5.9%	(6) 11.1%
Prolapse of iris	(0) 0	(0) 0
Iridocyclitis	(3) 5.9%	(7) 13.0%
Hemorrhage in A. C.	(3) 5.9%	(10) 18.5%
Delayed restoration of A. C. after 7th day	(3) 5.9%	(4) 7.4%
Late loss of A. C.	(3) 5.9%	(5) 9.3%
Total number of choroidal detachments	(3) 5.9%	(7) 13.0%
Retinal detachment	(1) 2.0%	(1) 1.9%
Secondary glaucoma	(1) 2.0%	(2) 3.7%
Incomplete wound closure		
Wound gape	0	(2) 3.7%
Filtering cicatrix	0.0%	(2) 3.7%
Total	(3) 5.9%	(4) 7.4%

* The number of complications in each category is too small for statistical analysis except for the hemorrhages in the anterior chamber (A. C.). Here the size of the experimental groups (51 and 54 cases) is too small to show the difference which in all probability exists.

It is significant that in every complication considered the incidence is higher with the keratome-scissors incision. That is, if one were to add up all the complications and say that of the 51 cases with knife incisions there were 23 complications, whereas in the 54 cases of the keratome-scissors operation there were 46 (approximately) complications, the difference between the total complications with the two methods would be highly significant.

principles of the McLean stitch as I have modified it, has proved most satisfactory to us, chiefly because it is appositional, nonpenetrating, can be placed after the incision and permits complete covering of the deep wound with a conjunctival flap. Analysis of our cases showed no significant difference in our results when one and when two sutures were used.

The insertion of sutures deep enough to be of real service, and they should engage fully one-half the thickness of the cornea and sclera, is difficult, especially with the needles now available. Postoperative reaction in eyes in which multiple deep sutures are used is greater and more

prolonged, as a rule; and their removal may be difficult, and at times followed by loss of chamber or by hyphema, as shown by Hughes and Owens. This has rarely occurred in our experience.

The Kalt-Stallard type of sutures is more easily inserted and removed, but apposition of the wound edges may be inaccurate and closure not so firm. The corneoepiscleral type of suture as we used it in some operations was ineffective, and study of our cases suggests that it actually prevented prompt and accurate apposition of the lips of the wound.

While statistical analysis of our results following the use of surgical gut and of those silk sutures showed no significant difference, I believe that silk is preferable.

CONCLUSIONS

Analysis of the postoperative complications and final results which we obtained after the knife and the keratome-scissors incisions has convinced us of the superiority of the knife incision. Healing after the knife incision appeared to be smoother and more rapid and was followed by fewer postoperative complications, especially hemorrhage into the anterior chamber, iridocyclitis, delayed restoration and late loss of the chamber, incomplete closure of the wound, choroidal separation and secondary glaucoma. Delayed restoration of the chamber, possibly due to an uneven incision and imperfect apposition of the edges of the wound, with subsequent leakage, and also increased trauma to the globe from the use of scissors, may account for the high incidence of complications we encountered after the keratome-scissors operation.

I do not wish to leave the impression that the keratome-scissors technic has been uniformly unsuccessful in our hands, for in 40 per cent of the cases the healing was without complication and the postoperative course uneventful. This is obviously a very low average and compares unfavorably with the series of extractions with the knife incision, after which healing was uncomplicated in approximately 75 per cent of the cases.

Evaluation of the "new operation," which seems destined to revive the age-old controversy that has waged back and forth since Daviel's time, must depend on the personal experience of the operator until the keratome-scissors method has been more fully explored and abundant statistical data have been brought to light.

When the keratome-scissors operation is used, adequate suturing of the deep wound is essential to prevent leakage of the wound. Deep sutures are also indispensable with either method of incision when the round pupil technic is employed. Improvement of the quality of

needles now available may reduce the trauma incident to their insertion. A complete conjunctival flap sufficient to cover the deep wound, which is sutured separately, has proved invaluable in our hands.

Our experience, based on a review of a total of 425 cases of the keratome-scissors extractions, has taught us much about this method. The keratome-scissors incision has been useful at times when the chamber was very shallow; however, the complications which have followed this technic have led us to abandon it as a routine procedure.

Dr. George Kambara, instructor in the department of ophthalmology, assisted in the review of the records for the keratome-scissors series of extractions.

MANAGEMENT OF STRICTURES OF THE LACRIMAL CANALICULI WITH POLYETHYLENE TUBES

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EPIPHORA, as the result of an obstruction in the drainage channels for the tears, is a persistent annoyance to many adults. The alleviation of this difficulty has been a problem that has frequently confronted both the ophthalmologist and the physician in general practice. In former years this problem has been managed chiefly through the insertion of metal probes into the channel extending from the lacrimal puncta to the opening of the nasolacrimal duct into the nose. Except in infants the various technics of probing have failed, as a rule, to effect permanent relief of the stricture or obstruction in the drainage channels, and the epiphora has returned after a temporary period of relief.

The perfection of the surgical technics of dacryocystorhinostomy has helped tremendously in the solution of the problem of epiphora among adults. Since the majority of obstructions to the normal flow of tears occur in the nasolacrimal duct, inferior to the lacrimal sac, dacryocystorhinostomy provides a means by which the tears are "short circuited," so to speak, into the nasal cavity. For obstructions located between the lacrimal puncta and the nasolacrimal duct dacryocystorhinostomy does not produce relief from tearing. It is with obstructions in this situation with which this paper is concerned.

Obstructions of the lacrimal drainage apparatus proximal to the lacrimal sac may be produced by a variety of conditions. Any disease process which produces a narrowing or an obliteration of the lumen of the lacrimal puncta and lacrimal canaliculi will produce epiphora. Chronic dacryocystitis which has been treated for a long period by repeated probing or lavage or both is a common cause. Burns of the skin in the region of the inner corner of the eye may lead to the formation of strictures. Changes in the skin of the face following roentgen treatment for malignant lesions may cause slow obliteration of the lumen of the lacrimal canaliculi. Trauma directly to the lacrimal canaliculi and adjacent areas may result from attacks on human beings by cats and dogs. The lumen of the canaliculus may be obliterated by the healing of such wounds. In the treatment of certain cases of keratoconjunctivitis sicca the lacrimal puncta and canaliculi are obliterated by electrodesiccation to conserve the scanty flow of tears. In many instances a remission in the disease process will result in epiphora because the tears are deprived of

their normal drainage channels. Regardless of the cause of the obstruction, adequate flow of tears again can be assured if the patency of the lower lacrimal punctum and the lower lacrimal canaliculus can be restored, provided that the channels distal to these points of obstruction are intact.

In the search for a suitable material that could be inserted into the tissues to reestablish communication between the conjunctival sac and the lacrimal sac and thus restore drainage of tears, it was decided to try a plastic that has been successfully utilized in the experimental anastomosis of the common bile duct, trachea and pelvic portion of the colon; as a dural substitute, and in venoclysis.[1] The physical properties of this substance, polyethylene or polythene,[2] have been extensively investigated by Grindlay and co-workers[1b-e] and by others.[3] In the form of a tube approximately 1 mm. in outside diameter and 50 mm. in length, and with a lumen of approximately 0.6 mm., polyethylene was utilized to reestablish the patency of an obstructed lacrimal canaliculus in the case to be reported.

REPORT OF A CASE

A woman aged 21 reported to the Mayo Clinic on April 25, 1949. Her chief complaint was excessive tearing from the right eye of about seven years' duration. There was no history of trauma to the eye or its adnexa, and in the patient's opinion the onset of the disorder of lacrimation had been spontaneous. The lacrimal drainage passages had been probed several times prior to examination at the Clinic, but no permanent relief had been obtained, and she gave a reasonably good history of abscess of the right lacrimal sac during this interval of repeated probing. At one time the patient stated that a thread had been passed from the lower right lacrimal punctum through the lacrimal drainage channels into the nose and brought out through the anterior naris so that the ends of the thread could be tied on the cheek. This thread was allowed to remain in position for approximately ten weeks, but after its removal the excessive tearing returned in one week and the lacrimal drainage passages again seemed obstructed.

On inspection of the eyes at the Clinic, epiphora of moderate degree from the right eye was evident. The right upper lacrimal punctum was absent. The right

1. (*a*) Guenther, T. A.; Grindlay, J. H., and Lundy, J. S.: New Flexible Capillary Tubing for Use in Venoclysis, Proc. Staff Meet., Mayo Clin. **22**:206-207 (May 14) 1947. (*b*) Brown, M. H.; Grindlay, J. H., and Craig, W. M.: Preliminary Report on Experimental and Clinical Studies with Polythene Film, ibid. **22**:453-456 (Oct. 1) 1947; (*c*) The Use of Polythene Film as a Dural Substitute: An Experimental and Clinical Study, Surg., Gynec. & Obst. **86**:663-668 (June) 1948. (*d*) Grindlay, J. H.: Method of Making Tubes of Polyethylene Film for Use in Anastomosis of the Common Bile Duct, Trachea, and Pelvic Colon, Surgery **24**:22-29 (July) 1948. (*e*) Grindlay, J. H., and Mann, F. C.: Surgical Uses of Polythene: An Experimental Study, Arch. Surg. **56**:794-812 (June) 1948. (*f*) Meyers, L.: Intravenous Catheterization, Am. J. Nursing **45**:930-931 (Nov.) 1945.

2. Manufactured by the Surprenant Manufacturing Company, Boston.

3. Ingraham, F. D.; Alexander, E., Jr., and Matson, D. D.: Synthetic Plastic Materials in Surgery, New England J. Med. **236**:402-407 (Mar. 13) 1947.

lower lacrimal punctum seemed slightly enlarged. A no. 1 Bowman silver probe was inserted into the right lower lacrimal punctum and passed along the right lower lacrimal canaliculus. The movement of the probe was stopped by an obstruction at the approximate junction of the lacrimal canaliculus and the lacrimal sac. Then the probe was withdrawn. A 26 gage hypodermic needle was inserted in the lower right lacrimal punctum and pushed along the lacrimal canaliculus. Some resistance to the movement of the needle was encountered, but with a slight push the point of the needle seemed to pass through the point of obstruction and to enter the lacrimal sac. Needles of increasing diameter were then utilized to enlarge the opening through the obstruction in the lacrimal canaliculus. It was finally possible to pass the no. 1 Bowman probe from the lacrimal punctum through the lacrimal canaliculus and into the lacrimal sac. An attempt to irrigate the lacrimal drainage passages was made, but the fluid would not pass into the nose. This indicated an additional obstruction somewhere in the right nasolacrimal duct. A diagnosis of

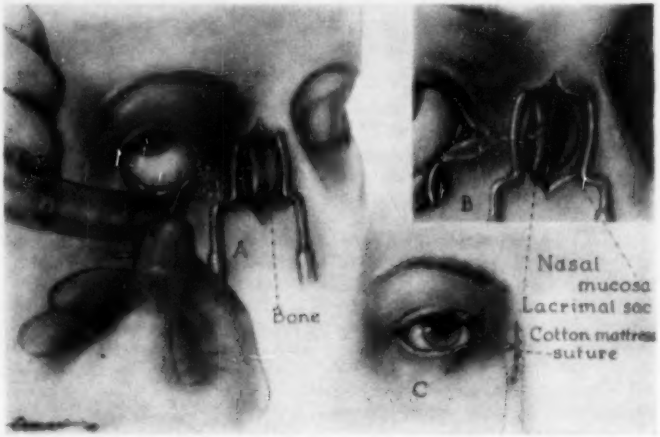

Fig. 1.—Reconstruction of lacrimal canaliculus with polyethylene tube. *A*, threading of polyethylene tube along lacrimal canaliculus and into lacrimal sac; *B*, insertion of cotton suture; *C*, positions of suture and polyethylene tube on completion of operation.

obstruction of the right nasolacrimal duct and stenosis of the right lower canaliculus was made.

On April 29, dacryocystorhinostomy was performed on the right side, with the use of local anesthesia. During the course of this surgical procedure, after the medial wall of the lacrimal sac had been removed and prior to the union of the lacrimal sac to the nasal mucosa by sutures, the polyethylene catheter was threaded through the lacrimal punctum and along the lacrimal canaliculus [4] until the leading

4. When this procedure is used, if the polyethylene tube is too flexible to permit easy insertion into the lumen of the lacrimal canaliculus, a silkworm gut style can be threaded into the lumen of the polyethylene tube. This will stiffen the tube so that its passage into the lacrimal sac will be facilitated. The style should be withdrawn before the silkworm gut has an opportunity to imbibe fluid.

tip of the catheter was visible in the lacrimal sac (fig. 1 *A*). About 2 mm. of the length of the catheter was allowed to protrude into the cavity of the lacrimal sac. The polyethylene catheter was anchored in this position by means of a double-armed no. 70 spool cotton mattress suture (fig. 1 *B*). Each needle arm of the suture was inserted into the lumen at the tip of the catheter protruding into the cavity of the lacrimal sac, then passed through the wall of the polyethylene catheter and the wall of the lacrimal canaliculus with a rotating motion so that the needles, about 1 mm. apart, punctured the skin directly anterior to the medial end of the lacrimal canaliculus (fig. 1 *B*). The cotton suture was tied snugly, but without undue pressure on the surface of the skin (fig. 1 *C*). With the suture tied, the polyethylene tube could not be rotated or moved more than 1 or 2 mm. in any direction within the canaliculus. The dacryocystorhinostomy was completed in the usual manner. A suitable length of the polyethylene catheter was allowed to protrude (fig. 2) from the lacrimal punctum so that it could be taped to the cheek without undue tension on the lower lid. The flexibility of the catheter permitted such a maneuver without producing ectropion of the lower lid.

The polyethylene catheter was left in this position for forty-five days (six and a half weeks). Almost daily the tube was irrigated with water by inserting a 26 gage hypodermic needle into the tip of the catheter, lying externally. The husband

Fig. 2.—Position of polyethylene tube in right lower lacrimal canaliculus in the case reported.

of the patient was instructed in this procedure, so that it was unnecessary to see the patient daily during this interval. The patient was provided with a collyrium to instil into the conjunctival sac as a prophylactic measure against conjunctivitis or secondary bacterial invasion of the lacrimal canaliculus. About one week after operation the epiphora of the right eye was greatly reduced and the tears seemed to be passing spontaneously through the lacrimal punctum and the lacrimal canaliculus, but outside the catheter. In about the fifth postoperative week a fistula developed around the tract of the cotton suture, so that a drop or two of tears would spontaneously appear and surround the knot of the suture. The knot of the suture would then tend to loosen, so that it was necessary to tighten the loops of the knot about twice weekly. In general, however, the postoperative period was uneventful; no infection appeared, and the tissues seemed perfectly tolerant of the polyethylene tube.

On the forty-sixth postoperative day one arm of the cotton suture was cut, the suture removed and the polyethylene tube pulled out of the lacrimal canaliculus and lacrimal punctum. After the removal of the polyethylene tube the tears continued to drain spontaneously into the nose via the lacrimal punctum, lacrimal canaliculus and dacryocystorhinostomy stoma. Epiphora did not recur. On the fourth day following the removal of the polyethylene catheter I was alarmed to find that a

no. 1 Bowman probe could not be passed along the lacrimal canaliculus. The probe was withdrawn, and no attempt was made to dilate the lacrimal canaliculus by forced passage of the probe.

Six months have passed since the removal of the polyethylene tube and cotton suture; no instrumentation or dilation of the lacrimal canaliculus has been necessary during this interval. The lacrimal drainage passages continue to function satisfactorily, and excessive tearing is no longer present, according to the patient. The fistula that had developed along the suture tract closed spontaneously after removal of the cotton thread.

COMMENT

Polyethylene, closely related to paraffin chemically, seemed to be ideally suited to the reconstruction of the lacrimal canaliculus. Polyethylene, like paraffin, does not seem to undergo physical or chemical

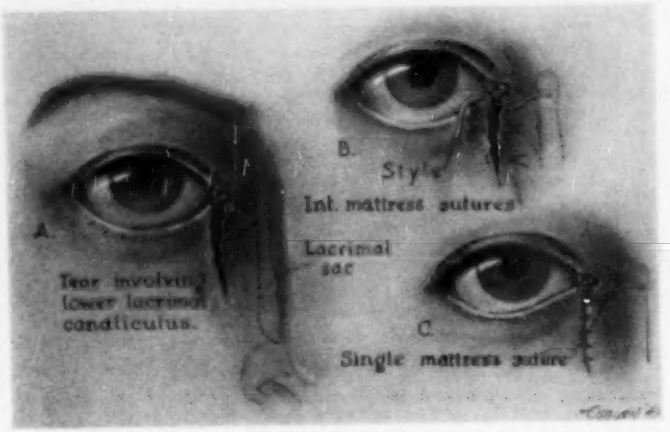

Fig. 3.—Reconstruction of post-traumatic defect in lower lacrimal canaliculus with polyethylene tube.

change when implanted in tissues, nor does it create any undesirable effects in the living tissues which surround it. Unlike paraffin, polyethylene is unaffected by boiling. In the case reported here, the tubing firmly held the cotton suture that was threaded through its wall, and this characteristic has been noted also by Grindlay and associates.[1b]

This material and the method of treatment described in this case may be suitable also for reconstruction of a lacrimal canaliculus that has become obstructed as the result of factors other than infection. In cases of trauma, in which the lacrimal canaliculus has been torn, the severed ends of the canaliculus might be brought together around the polyethylene tubing, as shown in figure 3 *A* and *B*. A cotton mattress suture should be inserted through the lumen of the polyethylene tube

(figs. 1 *C* and 3 *C*) to anchor it into position. In cases of children and infants,[5] in which protrusion of one end of the polyethylene tubing might not be desirable, the tubing might be cut so that it remained entirely within the canaliculus (fig. 3 *C*). In such cases the tubing could be removed later, with use of general anesthesia, by the exertion of digital pressure over its medial end.

In situations in which it is not deemed necessary to perform a dacryocystorhinostomy in addition to the insertion of the polyethylene tube, the stricture may be dilated and the tube inserted and sutured into position.

The length of time necessary for the retention of the polyethylene tubing must depend on the circumstances in the individual case and the judgment of the physician. Since the tissue response to polyethylene is practically nil, it has been possible to keep the tubing in the lacrimal canaliculus for forty-five days. If the tubing is removed too soon, there is a reasonable chance that the stricture or obstruction may recur.

A warning has been sounded by Ingraham and associates [6] that for the best results the polyethylene for the use in human tissues must be free of impurities.

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5. For use in infants and children, a smaller diameter of tubing (outside diameter 0.6 mm. and inside diameter 0.3 mm.) is available.

TONOGRAPHIC METHOD FOR MEASURING THE FACILITY AND RATE OF AQUEOUS FLOW IN HUMAN EYES

W. MORTON GRANT, M.D.
BOSTON

THE PURPOSE of this preliminary report is to describe a manner of utilizing the Schiötz tonometer to obtain a measure of the patency of the channels of aqueous humor outflow and of the steady state net rate of aqueous humor flow. It is believed that the method described here provides a means of discerning in what measure changes in intraocular pressure are due to change in facility of outflow or to change in net rate of aqueous humor formation. A subsequent report will describe the alterations in these factors which are effected in normal and in glaucomatous eyes by various medical and surgical influences.

The electronic Schiötz tonometer is electrically connected to an amplifier and recording galvanometer in such a manner that all measurements made by the tonometer are continuously and automatically recorded on a moving paper strip, such as is employed in electrocardiography. The apparatus is pictured in figure 1. The tonometer foot plate assembly is placed on the patient's cornea in the manner customarily employed for simple measurement of ocular tension but is allowed to remain there for five to six minutes. During this period there is a gradual decrease in ocular tension, which is permanently recorded on the paper strip, as shown in figure 2. The pulse wave and any incidental effects of respiration or eye movement on the ocular tension are also clearly reproduced.

From the recording are determined, by means to be described shortly, the steady state intraocular pressure before application of the tonometer, the intraocular pressure during the period the tonometer is resting on the eye and the decrease in volume of the eye during this period. From these figures are calculated, first, the average increment in intraocular pressure during the measurement (due to the weight of the tonometer) and the constant of proportionality between the pressure and the rate of volume loss. This constant represents primarily a measure of the facility with which fluid in the eye can leak or be forced out, expressed in terms of cubic millimeters of fluid per minute per millimeter

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

(mercury) of intraocular pressure, assuming the small pressure increment involved in the measurement to have an insignificant effect on the rate of formation of aqueous humor. An approximation of the total steady state rate of outflow, in cubic millimeters per minute, which in

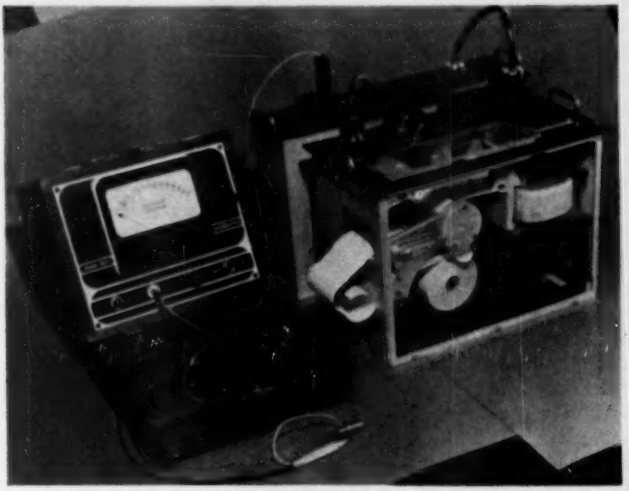

Fig. 1.—Electronic tonometer, amplifier and paper strip recording galvanometer employed for tonography.

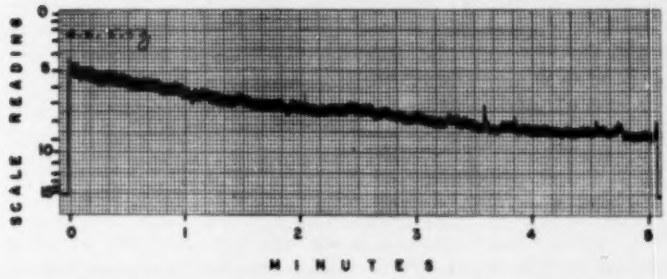

Fig. 2.—Typical tonogram of a normal human eye obtained during five minutes of recording.

a steady state also equals the net rate of aqueous humor formation, is then provided by the product of the steady state intraocular pressure and the pressure coefficient of outflow. The basis for these calculations will now be considered in more detail.

RELATION OF TONOMETRIC READING, INTRAOCULAR PRESSURE AND OCULAR VOLUME

When the Schiøtz tonometer is allowed to rest on a human eye in the usual manner, the intraocular pressure is raised because the cornea is indented and a small volume of fluid is displaced which can be accommodated elsewhere in the eye essentially only by a distention of the coats of the eye. The artificial pressure levels obtaining in eyes with the Schiøtz tonometer resting on them have been measured numerous times by other investigators, employing enucleated eyes which were connected by means of a cannula to a simple open manometer, and data have been obtained relating the tonometer scale readings with various weights on the plunger to the coexisting intraocular pressures. The most accurate of such data are those of Friedenwald.[1] These data are used in the present work to convert the tonometer scale readings which are graphically recorded on the moving paper strip into terms of the corresponding actual ("open manometer") intraocular pressure obtained during the recording. This intraocular pressure with the tonometer resting on the eye is, of course, greater than that existing in the absence of the tonometer. Ordinarily, and also for the purposes of the present work, it is desirable to know what the intraocular pressure was when the tonometer was not on the eye, and this information is obtainable from the standard calibration charts which accompany Schiøtz tonometers. Again, undoubtedly the most accurate data are those calculated by Friedenwald.[1]

For application of the method described here, the eye is assumed to exist in a steady state before application of the tonometer, with the intraocular pressure determined by the net rate of aqueous humor formation and the amount of resistance to escape of aqueous humor from the eye. Application of the tonometer is considered to disturb this steady state by increasing the intraocular pressure and increasing the rate of escape of fluid, presumably aqueous humor, from the eye. The pressure increment by which the conditions of equilibrium are disturbed is represented by the difference between the undisturbed original pressure, Po, and the artificially elevated pressure, P_T.

With increase in rate of escape of aqueous humor from the eye, the total ocular volume decreases at a rate corresponding to the difference between the rate of loss and the rate of formation of aqueous humor, that is,

Aqueous humor formation — aqueous humor loss = change in ocular volume

So far as the rate of formation remains unchanged, the rate of decrease

1. For use in the present work, Dr. Jonas Friedenwald made available detailed data obtained in 1940, and as yet unpublished. Previous data were published by Dr. Friedenwald in the *American Journal of Ophthalmology* (**20**:985-1024, 1937; **22**:375-383, 1939; **31**:935-944, 1948).

in ocular volume will equal the increase in rate of loss of aqueous humor. Experimental evidence, to be presented subsequently, indicates that the rate of formation is altered little by the small increase in pressure produced by application of the tonometer. Accordingly, pending the development of means for actual correction of any small change in rate of formation, in the present method the rate of decrease of ocular volume is taken as an adequate approximation of the increase in rate of loss of aqueous humor. Now ocular volume has been shown by Friedenwald to be a function of the logarithm of the intraocular pressure, and if adequate data for conversion were available the change in intraocular pressure found during the recording period could be converted into terms of change in ocular volume and rate of fluid outflow. Such data have been derived in the following manner:

With the tonometer resting on the eye at a given intraocular pressure, the cornea is somewhat indented by the foot plate and plunger, and the coats of the eye are in a certain state of distention. When there is a loss of fluid from the eye, the pressure decreases, the eye is less distended and indentation by the tonometer increases. Actually, the volume of the increase in indentation plus the volume of the decrease in distention must equal the volume of fluid lost from the eye, since dilute watery solutions are essentially incompressible. Fortunately, Friedenwald has calculated the volume of tonometric indentation for the whole range of conditions encountered in ordinary measurements.[1] Also, in the course of his measurements and calculations he has obtained for human eyes under tonometric distortion a reasonable approximation of the coefficient of rigidity and an expression relating intraocular pressure to distention volume. From his data have been calculated the combined change in corneal indentation and scleral distention volumes related to change in tonometer scale readings while the tonometer is on the eye.[2]

2. It is of some incidental interest to note that at the very outset of the recording procedure, when the tonometer is placed on the eye, the volume of the eye is momentarily the same at Po as at P_T, since the fluid contents are essentially incompressible, and that, similarly, after a period during which there has been loss of volume from expression of fluid, if the tonometer is removed from the eye there is momentarily an identical ocular volume with and without the tonometer, although the eye is of different shape under these two conditions. From the usual type of calibration curves for determining undisturbed ("closed manometer") intraocular pressure, one knows reasonably well what the pressure is immediately before and immediately after the tonometric or tonographic determination. At the same time, one has information on the total volume loss during the application of the tonometer from the data of table 1. Now the change in volume from just before to just after the period of application of the tonometer is essentially one of change in distention, which is, as has been seen, necessarily equal to the combined change of indentation and distention volumes under tonometric distortion. One has, therefore, information on both the change in pressure and the change in volume of the eye undistorted by

(Footnote continued on next page)

In table 1 the resultant data are presented for eyes with normal scleral rigidity. The volume value is arbitrarily set at zero in each column of the table to correspond to the zero scale reading. Change in volume during change in scale reading is equal to the difference between the corresponding values for volume read from the appropriate column for whatever tonometer weight is used throughout the recording. The quantitative accuracy of this value, and therefore of all the estimations of volume in this work, depends, of course, on the accuracy of Friedenwald's data.[1]

TABLE 1.—*Relation of Scale Readings to Change in Ocular Volume*

Schiøtz Scale Reading	Volume Change (Cu. Mm.) for Individual Tonometer Weights			
	5.5 Gm.	7.5 Gm.	10 Gm.	15 Gm.
0	0	0	0	0
1	3.1	2.6	2.4	2.0
2	6.3	5.4	4.8	4.1
3	9.5	8.2	7.3	6.1
4	12.7	11.0	9.9	8.3
5	16.0	13.8	12.1	10.4
6	19.5	16.7	14.6	12.5
7	22.8	19.7	17.3	14.8
8	26.3	22.9	20.1	17.2
9	29.9	26.1	22.8	19.6
10	33.7	29.3	25.7	22.2
11	37.3	32.6	28.7	24.8
12	41.2	36.0	31.7	27.6
13	45.3	39.6	34.7	30.5
14	49.4	43.4	38.2	33.5
15	50.7	47.3	41.5	36.7

One now has the means for deriving from the recorded information on the paper strip the following information: the steady state pressure, Po, before application of the tonometer, the amount of elevation or increment of pressure, ΔP, above the steady state pressure during the recording, and the resultant loss of fluid volume, ΔV, from the eye during the same period. As will be shown subsequently, the rate of loss of ocular volume, $\frac{\Delta V}{T}$, or increased escape of fluid during recording, is found to be directly proportional to the amount of increase in pressure, i. e.,

$$\frac{\Delta V}{T} = C \cdot \Delta P$$

or, in a more convenient expression, volume loss is proportional to the product of the pressure increment and the time of application, i. e.

$$\Delta V = C\,\Delta P \cdot T$$

the tonometer, and from this one can calculate the coefficient of rigidity for the normal, undisturbed eye. Determined in this manner, the coefficient of rigidity is essentially identical with that which is held to represent the condition of the eye when under compression by the tonometer, suggesting that distortion or ablation of the globe by the Schiøtz tonometer has little influence on the rigidity of the sclera.

The total change in ocular volume or loss of fluid which occurs from beginning to end of the recording becomes equal to the product of the changing pressure increment from beginning to end times the time, but this is found to be adequately represented by an arithmetical average of the pressure increment for successive half-minute intervals times the total time, i. e.,

$$\Delta V = C\,(Av.\,P_T - Po)\,T$$

The coefficient in which we are interested, C, which represents the rate at which fluid can be expressed from the eye by pressure, in terms of cubic millimeters per minute per millimeter (mercury) pressure, is obtained arithmetically from the expression

$$C = \frac{\Delta V}{(Av.\,P_T - Po)\,T}$$

Information on the net rate of flow of aqueous humor through the eye under steady state conditions can be obtained by utilizing the pressure coefficient, C, in conjunction with the estimated steady state pressure. Thus, at the steady state pressure, Po, when the net rate of aqueous humor formation and the rate of outflow, K, are equal, Po presumably represents the pressure required for the escape of aqueous humor at the rate K, owing to the resistance to outflow expressed by the pressure coefficient of outflow, C, i. e.,

$$K = Po \cdot C$$

It will be seen from experimental data to be presented that the net rate of flow of aqueous humor, K, for normal eyes arrived at in this manner from determinations of Po and C corresponds reasonably well with the generally accepted values which have been obtained by other methods.

APPARATUS

The Müller electronic tonometer has been adapted to recording by taking the alternating current voltage between the cathode of the 6J5 tube and ground, on the advice of the manufacturer, and rectifying this voltage to filtered direct current by means of a full wave selenium instrument rectifier (Conant type M) with a 10 microfarad (25 volt) electrolytic condenser across its output. This direct current voltage is connected to a direct current amplifier (Sanborn, model 124), operated at full amplification. The output of the amplifier drives a recording galvanometer (Sanborn, model 123) with special slow speed drive to give a paper movement of 30 mm. per minute. This arrangement gives essentially edge to edge recording on the paper for full scale swing of the tonometer needle. To obtain smooth movement of the tonometer plunger, as evidenced by a good pulse wave in the recording, it was found helpful to buff the sliding metal parts of the tonometer to a higher luster than that furnished by the manufacturer. At each recording run, a calibration scale is recorded on the paper strip by manually positioning the tonometer plunger to bring the tonometer needle successively to each full unit of the tonometer scale for a few seconds. Any point on the recording from the eye is evaluated by reference to this recorded calibration scale.

RESULTS

A typical recording of five minutes duration from a normal human eye is reproduced in figure 2. Recordings of this nature are feasible over considerably longer periods and have been made for as long as twenty-three minutes, limited only by the tonometer's eventually going off scale.

The relation of pressure increment, time and volume loss during a single recording on a typical normal eye is presented in figure 3, in which the progressive loss of volume, ΔV, is plotted against the product of pressure increment, ΔP, and time. From the approximately linear relation which is apparent, it can be deduced that the loss of volume

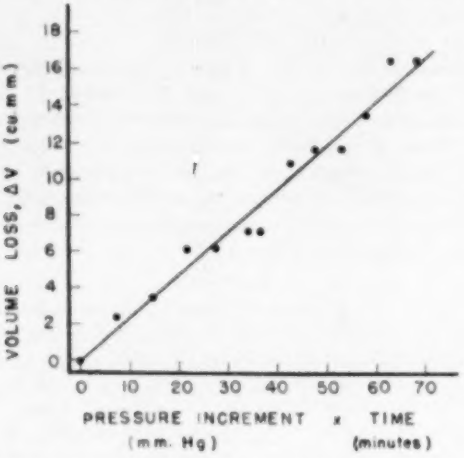

Fig. 3.—Relation of progressive loss of volume from a normal eye to the product of the intraocular pressure increment induced by the weight of the Schiøtz tonometer (with 5.5 Gm. weight) and its duration of application.

is proportional to the product of the pressure increment and its duration.

A representation of the relation of rate of loss of volume, $\Delta V/T$, to the pressure increment, Av. $P_T - Po$, which is induced by the weight of the tonometer, is given in figure 4. The data in this figure were obtained by several runs on the same normal eye, using four different plunger weights (5.5, 7.5, 10 and 15 Gm.) to extend the range of pressures employed. It appears that for the pressure range which was studied the rate of loss of volume was proportional to the increase in intraocular pressure to which the eye was subjected. It is of considerable interest to observe also that the experimental points in this figure

which represent progressive loss of volume and decrease in pressure extrapolate toward zero rate of volume loss at zero pressure increment, indicating a tendency to return during tonographic recording to the pressure, *Po*, which obtained in the original normal steady state. It may be deduced that the equivalence of flow in and flow out, which is disturbed by application of the tonometer, tends to reestablish itself as the pressure drops toward *Po* while the tonometer continues on the eye. If the tonometer was removed from the eye after a period of recording, the intraocular pressure was then lower than normal; and if periodic brief measurements were made during the period of spontaneous recovery in a normal eye, a similar approach to *Po* was observed with diminishing

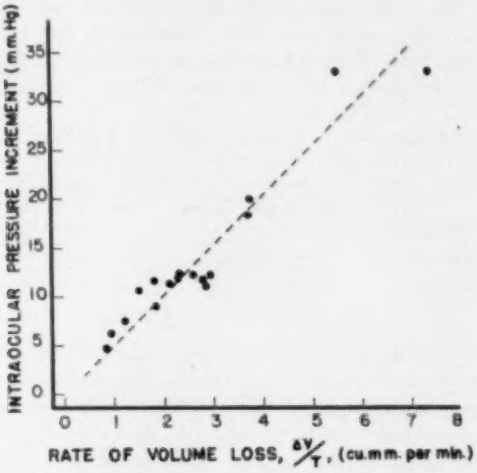

Fig. 4.—Relation of the rate of loss of volume from a normal eye to the increment in intraocular pressure produced by the weight of the Schiøtz tonometer.

rate of regain of volume to zero, again reestablishing the steady state pressure, *Po*. The latter observations have not been included in the figure, both in the interest of simplicity and because they are not entirely germane to the methods of measurement primarily under consideration.

The results of measurements on a series of normal eyes of *C*, the rate of expression of fluid per millimeter of pressure, and of *K*, the inferred approximate net rate of aqueous flow, at the steady state are presented in table 2.

Tonographic measurements were also made on enucleated normal human eyes which had been immersed in saline solution long enough to have established a fairly constant intraocular pressure. In these eyes the intraocular pressure which obtains during bathing in sodium chloride

solution is a function of the osmotic pressure of the bathing solution. When the rate of osmotic gain of water and the rate of leakage of aqueous humor are nearly equilibrated, as indicated by a very small rate of spontaneous change of intraocular pressure, an approximation of steady state conditions exists. Values for *C* which are obtained under these conditions average close to the values obtained for normal living human eyes.

CORRELATIVE EXPERIMENTS

Additional experiments, intended to aid in determining the validity of the present methods of measurement and calculation, were carried out thus: Recordings were made on rabbit eyes in the same manner as for human eyes; but, because adequate conversion data are not yet available for the pressure and volume relations of this species, only qualitative, or at best semiquantitative, measurements have been possible. However, by comparison of relative rates of change in the tonometer

TABLE 2.—*Measurements of Pressure Coefficients and Net Rates of Flow*

	Pressure Coefficient of Outflow, C (Cu. Mm./Minute/Mm. Pressure)	Steady State Net Rate of Aqueous Flow, K (Cu. Mm./Min.)
34 normal human eyes	Range, 0.15 to 0.34; average, 0.243	Range, 1.3 to 5.4; average, 2.66
14 measurements on a single eye	Range, 0.15 to 0.24; average, 0.196	Range, 2.4 to 4.5; average, 3.35
8 measurements on another single eye	Range, 0.17 to 0.26; average, 0.245	Range, 2.0 to 3.1; average, 2.73

reading on individual eyes under various experimental conditions, useful information has been derived. In normal rabbit eyes the nature of the decline in pressure during application of the tonometer resembles that in human eyes. When a rabbit is dead, and therefore its aqueous humor formation is diminished, the rate of decline of ocular volume during tonographic measurement, as would be expected, is distinctly greater than that during life. On the other hand, if the aqueous humor of a dead rabbit eye is replaced by a viscous aqueous solution of methyl cellulose, the decline in pressure is very much slowed. Similarly, if aqueous humor outflow in the living eye is impeded by injection of methyl cellulose into the anterior chamber, persistent glaucoma is produced, and the tonographic rate of decline is much reduced.

The rate of fluid outflow from eyes of dead rabbits at various intraocular pressures was determined by means of a simple open manometer and capillary flow meter connected with a needle in the anterior chamber. It was found that the rate of outflow from these eyes was directly proportional to pressure over the range measured of 20 to 60 mm. of mercury.

COMMENT

It has long been known that pressure on the eye would cause a temporary fall in intraocular pressure, and it has been noted several times that in glaucomatous eyes the decrease in intraocular pressure on repeated or sustained tonometry is generally not so great as in normal eyes. In such previous observations no attempt was made to utilize the knowledge of the decrease in intraocular pressure to provide quantitative information on rates of aqueous humor flow. However, after the present method had been developed, I learned from Dr. Friedenwald that Moses and Bruno had previously obtained information on progressive changes in volume in the eye in response to sustained compression with the Schiøtz tonometer. Dr. Moses furnished a prepublication description of their work, which is now in print.[3] According to this description, Moses and Bruno employed the electronic tonometer with periods of application of only one to two minutes, and read or obtained a photographic record of the movement of the tonometer needle during this time. They made estimates of the rate of volume loss from the eye and related this to total intraocular pressure during measurement. However, in their estimate of change of volume they considered only the change in corneal indentation by the tonometer and neglected the change in scleral distention, which is of similar magnitude. They did not utilize their data to calculate pressure coefficients of outflow or steady state net aqueous humor flow. The short period which they employed for measurement would seem to be disadvantageous in the light of experience with the longer electronic tonographic recordings, for not infrequently during the initial one-half to one minute of recording the ocular tension may behave somewhat erratically as compared with the relatively consistent rate of change which is recorded in subsequent minutes.

The principal questions which require discussion in connection with the validity of the method of measurement described in the present report concern the interpretations of the data rather than the instrumental technic. It is important to establish whether the fluid expressed from the eye by artificially increased pressure is in fact the aqueous humor, and whether the decrease in ocular volume which is observed is attributable in significant degree to expression of blood from the intraocular vascular bed or to suppression of formation of aqueous humor. That the change in ocular volume under compression is primarily a function of facility of escape of aqueous humor is indicated by the observations which were made on living and on dead normal rabbit eyes, as well as on eyes with artificially viscous aqueous humor. Thus the rate of tonographic decline was even greater in dead eyes in which

3. Moses, R. A., and Bruno, M.: The Rate of Outflow of Fluid from the Eye Under Increased Pressure, Am. J. Ophth. **33**:389-397, 1950.

the formation of aqueous humor had previously been arrested and the vascular bed had collapsed than in living eyes. Furthermore, by repletion of the aqueous humor in dead eyes by injecting saline solution, the curves could be repeated, and by substitution of methyl cellulose solution they could be strikingly altered, as they could in life by the same procedure. Further evidence that expression of blood or suppression of formation of aqueous humor contributes little to the changes in ocular volume which are measured in normal human eyes is furnished by the observation that the pressure coefficients of outflow are of the same magnitude for normal eyes as for eyes which are dead and enucleated, and therefore devoid of a blood circulation and a vital mechanism of aqueous humor formation. It is concluded for the present, until better evidence can be adduced, that in the method of measurement described in this report it is principally the increased outflow of aqueous humor that is measured and that the inaccuracy introduced by expression of blood or depression of inflow is probably small.

SUMMARY

A continuous automatic recording of the ocular tension is obtained for periods usually of five to six minutes from an electronic paper strip recorder connected to a commercial electronic Schiøtz tonometer while the foot plate and plunger assembly rests on the cornea. From these data are determined the steady state pressure, the pressure during the measurement procedure and the volume of fluid expressed from the eye. The rate of volume loss is proportional to the increment of pressure above the steady state pressure. A coefficient for the facility of aqueous humor outflow is calculated in terms of cubic millimeters per minute per millimeter (mercury) of pressure, yielding values of 0.15 to 0.34, with an average of 0.243, for normal human eyes, assuming on the basis of evidence presented that factors other than increased outflow of aqueous humor contribute little to the measured volume loss. From this coefficient and the steady state intraocular pressure is calculated the rate of outflow under steady state conditions, this rate being considered equal to the net rate of aqueous humor formation under those conditions. Values for normal eyes varied from 2.3 to 5.4 cu. mm. for 34 eyes, with an average of 3.66 cu. mm. per minute. This method is believed to present a means for discerning in what measure alterations of steady state intraocular pressure are due to changes in resistance to outflow or in what measure to changes in net rate of aqueous humor formation. Applications which are being made of the method include investigations of the mechanisms of glaucoma and of the effects of various medical and surgical influences in normal and in glaucomatous eyes.

243 Charles Street (14).

Miss Elizabeth O. Cushing has assisted in all aspects of this investigation, and Dr. Robert R. Trotter gave assistance in carrying out preliminary studies.

A UNIFIED CONCEPT OF AQUEOUS HUMOR DYNAMICS AND THE MAINTENANCE OF INTRAOCULAR PRESSURE

An Elaboration of the Secretion-Diffusion Theory *

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AQUEOUS humor dynamics deals with the movement of various components of the plasma into and out of the posterior and anterior chambers of the eye and with the forces that result from this movement. It is also concerned with the movement of substances that may be manufactured by the tissues of the eye.

The problem of aqueous humor dynamics is complicated predominantly by the number of separate anatomic regions of the eye involved and by the fact that these regions are separated from the plasma by several barriers, each having different physiologic properties. Owing to the complexity of the subject, usually only one aspect has been investigated at a time. For example, separate studies have been performed on (1) the physical and chemical characteristics of the aqueous humor, (2) the dynamics of this fluid in the anterior chamber and (3) the dynamics of aqueous humor in the posterior chamber, or, more especially, the function of the ciliary body in the "formation" of aqueous humor (secretory process). Yet the movement of dissolved substances in one region of the eye and the pressures produced are dependent on those in all the other regions. Consequently, a comprehensive understanding of aqueous humor dynamics requires consideration of the problem as a whole. The purpose of this paper, utilizing new experimental data, is to integrate available data into a unified concept.

For convenience of presentation, results of previous studies will be considered under the headings of osmotic pressure and composition of aqueous humor relative to plasma, dynamics of this fluid in the anterior chamber and nature of the secretory mechanism of the ciliary body. All data presented, unless otherwise indicated, are derived from experiments on rabbits, since quantitative information obtained under physiologic conditions for this species is the most complete.

From the Howe Laboratory of Ophthalmology, Harvard Medical School.
Supported in part by a grant from the Snyder Ophthalmic Foundation, Inc.

* Kinsey, V. E., and Grant, W. M.: The Secretion-Diffusion Theory of Intra-Ocular Fluid Dynamics, Brit. J. Ophth. **28**:355, 1944.

OSMOTIC PRESSURE AND CHEMICAL COMPOSITION OF AQUEOUS HUMOR AND PLASMA

Knowledge of the relative osmotic pressures of aqueous humor and plasma is of use indirectly in elucidating the problem of aqueous humor dynamics because it can reveal whether the aqueous humor is a dialysate of plasma; i. e., it can indicate whether the total expenditure of energy required for the production of aqueous humor is more than can be derived from the blood pressure. Similarly useful is knowledge of the relative chemical compositions of aqueous humor and plasma because it indicates the particular components of the plasma which require energy for their transfer to the posterior and/or the anterior chamber.

The osmotic pressure and chemical composition of aqueous humor and arterial blood (plasma), withdrawn from the anterior chamber and the heart of rabbits at approximately the same time, have been determined by Kinsey.[2] In freshly drawn samples the osmotic pressure of aqueous humor exceeded that of plasma by approximately 3 millimoles per kilogram of water equivalent of sodium chloride. In pooled samples, however, the osmotic pressures of aqueous humor and plasma and the total concentrations of dissolved substances determined chemically (table 1) were found to be approximately equal. The difference in osmotic pressure observed in fresh and in pooled samples suggested that some change in either aqueous humor or plasma occurred during the time required to prepare the pooled samples. Since the osmotic pressures of aqueous humor and plasma in the freshly drawn samples would be expected to be more representative of those in vivo, the values obtained on the fresh samples will be used in this paper.

The values for the total concentration of dissolved substances, despite any changes which may have resulted from the pooling operation, appear to be accurate to about 2 per cent, so that, for all practical purposes, they represent adequately the chemical composition of aqueous humor and plasma.

Most of the constituents of aqueous humor are not in equilibrium with those of plasma; i. e., their concentrations differ from those expected on the basis of the Gibbs-Donnan equilibrium (table 1). For example, in the case of the anions in aqueous humor, the concentration of chloride is less than that of the plasma, and the concentrations of bicarbonate, ascorbate and lactate are all significantly in excess of those in the plasma. The concentrations of cations, chiefly sodium, in aqueous humor appear to be slightly in excess of those in the plasma; i. e., sodium has a steady state concentration ratio of 0.98, instead of the theoretic 0.96. The concentrations of nonelectrolytes in aqueous humor are lower than in plasma, instead of being equal.

1. Footnote deleted.

2. Kinsey, V. E.: The Chemical Composition and the Osmotic Pressure of the Aqueous Humor and Plasma of the Rabbit, J. Gen. Physiol., to be published.

Results of the relative osmotic pressure determinations on aqueous humor and plasma (freshly drawn samples) also indicate that the constituents of aqueous humor are not in equilibrium with those in plasma and therefore the aqueous humor cannot be a simple dialysate.

Knowledge of the composition of aqueous humor in the posterior chamber is limited. The concentration of ascorbic acid in the aqueous humor in this chamber is about 1.4 times that in the fluid in the anterior

TABLE 1.—*Composition of the Aqueous Humor and Plasma of the Rabbit*

Dissolved Substance	Aqueous Humor (73 Eyes) mM/Kg. H_2O	Plasma (Arterial) (30 Animals) mM/Kg. H_2O	Ratio Aqueous/Plasma
Anions			
Chloride	107.9	113.8	0.95
Bicarbonate*	31.9	21.9	1.45
Ascorbate	1.2	0.1	12
Lactate	8.8	6.6	1.3
Phosphate	0.7	1.2	....
Sulfate†	0.6	1.2	....
Protein	< 0.05	2.0 (approximately)	....
Total	151.1	146.8	1.04 (diffusible ions only)
Cations			
Sodium	143.0	146.0	0.98
Potassium	4.7	4.8	....
Calcium (diffusible)	1.4	1.8	....
Magnesium‡	0.5	0.9	....
Total	149.6	152.5	0.981
Nonelectrolytes			
Carbonic acid	1.0	1.2	....
Nonprotein nitrogen	11.1	11.3	....
Glucose	5.6	6.6	....
Total	17.7	19.1	....
Grand total	318.4	319.4	....
Osmotic pressure (mM/L. equiv. NaCl)	155.0	156.4	....
	Total Solids in Plasma 7.2%		

* Average bicarbonate content determined separately in aqueous humor from 20 other eyes and 11 samples of plasma was 34.1 and 25.6 millimoles per kilogram of water, respectively.
† Data from W. Heubner and R. Meyer-Bisch (Ueber den Sulfatgehalt im Blutserum und Kammerwasser, Biochem. Ztschr. **126**: 184, 1926).
‡ Based on determinations performed on samples obtained from 13 other rabbits.

chamber,[3] and the concentration of chloride and osmotic pressure of aqueous humor in these two chambers are essentially equal.[2]

DYNAMICS OF AQUEOUS HUMOR IN THE ANTERIOR CHAMBER

The problem of aqueous humor dynamics in the anterior chamber involves the rates, paths and mechanism by which various components of aqueous humor move between this chamber and the iris, posterior chamber, cornea and lens. This problem has been investigated by

3. Kinsey, V. E.: Dehydroascorbic Acid: Ascorbic Acid in the Aqueous Humor of Rabbits, Am. J. Ophth. **33**:257, 1950.

Kinsey and co-workers,[4] who used isotopes of some of the constituents of aqueous humor to determine the paths and rates of transfer into and out of the anterior chamber. Deuterium oxide (heavy water) was used to trace the movement of ordinary water. This substance was injected into the blood stream, and its rate of accumulation in the anterior chamber was determined. From these data the rate of movement of ordinary water into and out of this chamber was calculated to be equivalent to approximately 20 per cent per minute of the total quantity of water present in the anterior chamber. This rate corresponds to 50 microliters of aqueous humor per minute. Similar measurements obtained with radioactive sodium and chloride indicated that the rate of movement of these ions into and out of the anterior chamber is equivalent to approximately 1.1 per cent per minute of the total quantity of sodium and chloride present. This rate corresponds to only 2.75 microliters of aqueous humor per minute.[4c] Thus, water, sodium and chloride do not enter or leave the anterior chamber at rates proportional to their relative concentrations in aqueous humor. In other words, aqueous humor, as found in the anterior chamber, is not "formed" as a whole, i. e., entirely by bulk movement from the posterior chamber.

Kinsey and Grant [5] pointed out that while the independent rates at which water, sodium and chloride enter and leave the anterior chamber would be compatible with the thesis that aqueous humor is a simple dialysate of plasma (i. e., water is diffusing back and forth between the anterior chamber and the blood at one rate and sodium and chloride at another) these differential rates would also support the concept that some aqueous humor is lost from the anterior chamber by flow, a process requiring expenditure of energy. Thus, solely from a knowledge of the rates of movement of water and salts, it is not possible to determine whether the aqueous humor is a static or a dynamic fluid. From a formulation of aqueous humor dynamics which stated, in effect, that nonmetabolized substances diffusing from the blood to the intraocular fluid would be deficient in the aqueous humor provided some of this fluid was lost by flow, and from measurements of the degree of deficiency of urea, Kinsey and Grant [5] deduced that aqueous humor leaves the anterior chamber by flow at a rate of approximately 4 micro-

4. (*a*) Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**:242 (Feb.) 1942. (*b*) Kinsey, V. E.; Grant, W. M.; Cogan, D. G.; Livingood, J. J., and Curtis, B. R.: Sodium, Chloride and Phosphorus Movement and the Eye, ibid. **27**:1126 (June) 1942. (*c*) Kinsey, V. E., and Bárány, E.: The Rate of Flow of Aqueous Humor: II. Derivation of Rate of Flow and Its Physiologic Significance, Am. J. Ophth. **32**:189, 1949.

5. Kinsey, V. E., and Grant, W. M.: The Mechanism of Aqueous Humor Formation Inferred from Chemical Studies on Blood-Aqueous Humor Dynamics, J. Gen. Physiol. **26**:131, 1942.

liters per minute. Subsequently, Bárány and Kinsey [6] determined the rate of outflow of aqueous humor by direct experiment. These investigators measured the rate at which several relatively large organic molecules left the anterior chamber and found that the rate of flow was 1.1 per cent per minute of the total amount of aqueous humor, or 2.75 microliters per minute. This rate is identical with that for the disappearance of sodium and chloride from the eye! Hence, Kinsey and Bárány [6c] concluded that sodium and chloride leave the anterior chamber only by flow. Moreover, since diffusion is a two way process, they concluded that no sodium or chloride can enter the anterior chamber by diffusion. This observation indicated that, while permitting passage of water, the iris is impermeable to sodium and chloride. These ions, therefore, must enter the anterior chamber from the posterior chamber by a flow process.

Kinsey and Bárány [6c] also pointed out that the same conclusion concerning the mode of entrance (and exit) could be drawn for any substance that can be shown to disappear from the anterior chamber at a rate corresponding to the rate of flow of aqueous humor. Substances tested, having rates of disappearance equal to the rate of outflow, are all electrolytes and include thiocyanate,[7] phosphate [8] and ascorbic acid,[9] in addition to sodium and chloride. A different conclusion must be drawn for substances that disappear at rates greater than the rate of outflow (it being assumed that no substance can leave the anterior chamber at a rate significantly lower than the rate of outflow). Substances tested having these rates are all nonelectrolytes and include urea,[6c] ethyl alcohol [10] and glucose.[11] These substances, therefore, are believed to leave the anterior chamber by diffusion as well as by flow out at the angle and consequently must enter the anterior chamber by diffusion in addition to flow from the posterior chamber. The relative contribution of diffusion and flow to the total loss of any substance from the anterior chamber can be illustrated in the case of water. Of the total movement of water out of the anterior chamber (50 micro-

6. Bárány, E., and Kinsey, V. E.: The Rate of Flow of Aqueous Humor: I. The Rate of Disappearance of Paraaminohippuric Acid, Radioactive Rayopake and Radioactive Diodrast from the Aqueous Humor of Rabbits, Am. J. Ophth. **32**:177 (June, pt. 2) 1949.

7. Kinsey, V. E., and Grant, W. M.: Further Chemical Studies on Blood-Aqueous Humor Dynamics, J. Gen. Physiol. **26**:119, 1942.

8. Palm, E.: On the Phosphate Exchange Between the Blood and the Eye, Acta ophth., 1948, supp. 32, p. 1.

9. Kinsey, V. E., and Bárány, E.: Unpublished data.

10. Palm, E.: On the Passage of Ethyl Alcohol from the Blood into the Aqueous Humour, Acta ophth. **25**:139, 1947.

11. Harris, J. E., and Gehrsitz, L. B.: The Movement of Monosaccharides into and out of the Aqueous Humor, Am. J. Ophth. **32**:167 (June, pt. 2) 1949.

liters per minute), 2.75 microliters a minute leaves by flow and 47.25 microliters a minute leaves by diffusion.[12] Thus, approximately 47.25 microliters of water a minute enters the anterior chamber by diffusion, primarily through the iris, and approximately 2.75 microliters of water a minute enters by flow, along with sodium and chloride, from the posterior chamber. In making this estimation, it is assumed that the concentrations of sodium and chloride are approximately equal to those of the aqueous humor of the posterior and the anterior chamber.

The general relation between the rate of disappearance of substances from the anterior chamber, i. e., by both flow and diffusion, and the ratio of their relative concentrations in the aqueous humor and plasma under steady state conditions have been calculated by Kinsey and

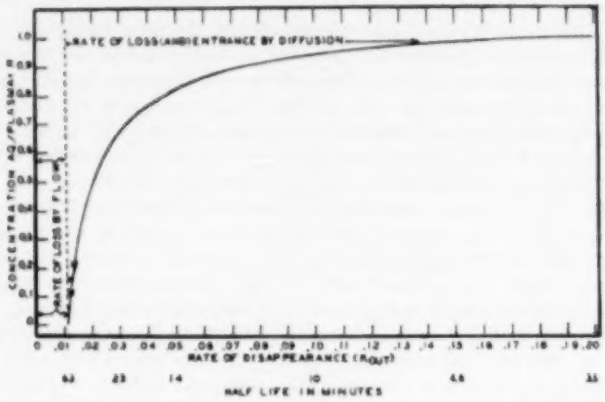
RATE OF LOSS/AND ENTRANCE BY DIFFUSION
CONCENTRATION AQ/PLASMA
RATE OF LOSS BY FLOW
RATE OF DISAPPEARANCE (Rout)
HALF LIFE IN MINUTES

Fig. 1.—Relation between the rate of disappearance of substances from the anterior chamber by both flow and diffusion, and the ratio of their relative concentrations in the aqueous humor and plasma under steady state conditions.

Bárány [6c] and are shown in figure 1.[13] The broken perpendicular line represents substances that enter and leave the anterior chamber by flow only. The rate of disappearance of these substances never exceeds the rate at which aqueous humor disappears by bulk flow, irrespective of the steady state ratio. The curved line represents substances that leave by both flow and diffusion. The rate of disappearance of these sub-

12. Friedenwald (personal communication to the author) pointed out that about 5 per cent more water diffuses into the eye than diffuses out, i. e., a ratio of 50 to 47.25 microliters, but that the total inward pressure exceeds the outward pressure by less than 0.1 per cent (a ratio of about 945,000/944,850 mm. of mercury).

13. The curved line is corrected to account for some solute entering the aqueous humor along with water. (For details see a previous article.[6c])

stances will always be greater than the rate at which they are lost by flow by an amount equal to the rate of loss by diffusion.

Reference to the graph, therefore, permits deductions to be drawn concerning the mode of entrance of any nonmetabolized substance whose rate of disappearance and steady state ratio of distribution are known. Use of the graph in determining how a substance enters the anterior chamber can be illustrated by applying the data already cited for sodium and urea. The steady state ratio of concentration of sodium is approximately 1, and the rate of disappearance from the anterior chamber is 1.1 per cent per minute of the total quantity of sodium present. These coordinates fall only on the perpendicular line. Hence, sodium enters

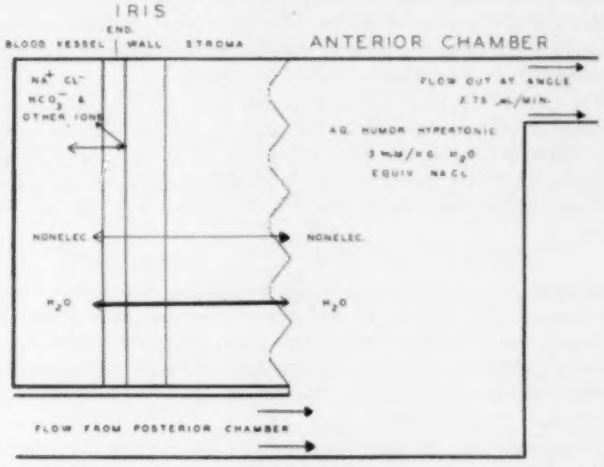

Fig. 2.—Movement of various substances from the anterior chamber to and from the blood.

the anterior chamber by flow only. The steady state ratio of concentration of urea is approximately 0.8, and the rate of disappearance from the anterior chamber is about 4 per cent per minute of the total quantity of urea present. These points fall only on the curved line. Thus, urea enters by both flow and diffusion, the contribution of diffusion being given by the distance to the right of the perpendicular line. The greater proportion of this substance enters by diffusion.

The dynamics considered thus far are illustrated schematically in figure 2. The solid arrowheads in the figure indicate direction of net transfer. Aqueous humor is shown to flow into the anterior chamber from the posterior chamber, where there is a diffusional exchange of water and nonelectrolytes from the blood vessels of the iris. The resul-

tant fluid is then shown to flow out of the anterior chamber at the angle. While the drawing indicates that the electrolytes are prevented from entering the anterior chamber from the iris by the wall of the blood vessel, this site of blockage is an assumption; the exact anatomic structure which is impermeable to these ions is not known.

The substances contributed by the lens to the aqueous humor have not been determined quantitatively, but it is believed that lactic acid, resulting from the metabolism of glucose, diffuses from the lens into the anterior and posterior chambers. Recent evidence in this laboratory indicates that aqueous humor also contains an excess of pyruvate (approximately 3.5 mg. per hundred cubic centimeters, compared with 2.5 mg. per hundred cubic centimeters in the plasma). This compound is also probably produced by the lens. The total exchange of these metabolites, however, is relatively small compared with the movement of compounds between aqueous humor and blood.

The flow of aqueous humor from the posterior chamber, through the anterior chamber and out at the angle of the eye requires energy. This energetic process has been defined as secretion.[86] The possible mechanism by which substances are secreted into the posterior chamber has been studied extensively and will be discussed in the following section.

SECRETORY MECHANISM OF THE CILIARY BODY

Whereas it has been possible to measure directly the rates of transfer of substances into and out of the anterior chamber and to infer the mechanism by which such transfer takes place, indirect means have been employed to study the dynamics of the aqueous humor in the posterior chamber, including the special function of the ciliary body in the production of aqueous humor.

Friedenwald and Stiehler[14] approached the problem by studying various properties of the ciliary body to determine whether there is any direct evidence of a secretory mechanism that could energetically transfer substances from blood into the posterior chamber.

These workers observed that the ciliary body exhibits irreciprocal permeability to positively and negatively charged dyes; the former pass from the stroma to the epithelium, and the latter pass from the epithelium to the stroma. This irreciprocal permeability depends on the presence of oxygen and can be abolished by certain poisons. The barrier at which acid dyes (anions) are prevented from penetrating the epithelium and basic dyes (cations) from penetrating the stroma lies at the junction of the epithelium and the stroma. This barrier is capable of being

14. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

reversibly oxidized and reduced and possesses a negative charge. No membrane to which these properties can be attributed is found histologically, but Friedenwald suggested that the barrier may be a monomolecular layer.

Friedenwald and Stiehler observed that the oxidation-reduction potential of the epithelium is +100 millivolts and that of the stroma —130 millivolts. The difference in potential is also dependent on the presence of oxygen and can be abolished by poisons, such as cyanide. This observation suggested that the potential is maintained by enzyme systems. The epithelium was shown to contain both cytochrome–cytochrome (indophenol) oxidase and dehydrogenase systems, whereas the stroma was found to contain only a dehydrogenase system. At least two, and probably three, substances (ascorbic acid, epinephrine and glutathione) are believed to act as mediators between the enzyme systems.

Friedenwald postulated that the irreciprocal permeability of the ciliary body is dependent on an electric current that transfers water and cations from the stroma to the epithelium, and anions from the epithelium to the stroma. He suggested that the source of energy for this current is supplied by differences in the aforementioned oxidation-reduction processes in the epithelium and stroma. The electric circuit is completed by transfer of electrons through the barrier, presumably by reversible oxidation and reduction of the barrier.

More recently Friedenwald [15] illustrated schematically how redox interaction between the stroma and the epithelium could lead to an electric circuit. Assuming that the oxidative cycle begins with the oxidation of cytochrome oxidase by molecular oxygen, with the transfer of electrons from the enzyme to oxygen, he suggested:

(1) Reduced cytochrome oxidase + $\frac{1}{2}O_2 \rightarrow$ oxidized cytochrome oxidase + $O^=$

(2) $O^= + H_2O \rightarrow 2OH^-$

The hydroxyl ions, he assumed, react with carbon dioxide to form bicarbonate ions.

(3) $2OH^- + 2CO_2 \rightarrow 2HCO_3^-$

The oxidized cytochrome produced in the system, he postulated, will be reduced by the barrier, which, in turn, becomes oxidized, only to be returned to its original reduced state by the stroma. The stroma provides electrons for this reduction at the expense of oxidation of a metabolite, according to the formula:

(4) $RH_2 - 2e \rightarrow R + 2H^+$

15. Friedenwald, J. S.: Dynamic Factors in the Formation and Re-Absorption of Aqueous Humour, Brit. J. Ophth. **28**:503, 1944; The Formation of the Intraocular Fluid, Am. J. Ophth. **32**:9 (June, pt. 2) 1949.

The excess hydrogen ions are presumed to react with bicarbonate to form carbon dioxide.

$$(5)\ 2H^+ + 2Na^+ + 2HCO_3^- \rightarrow 2Na^+ + 2H_2O + 2CO_2$$

Friedenwald pointed out that the net result of one cycle involving the reduction of one atom of oxygen in the epithelium and the oxidation of two atoms of hydrogen in the stroma gives rise to two incompletely balanced anions in the epithelium and two incompletely balanced cations in the stroma. To maintain electrical neutrality, anions would be transferred from the epithelium to the stroma, or cations from the stroma to the epithelium, or both.

Friedenwald concluded that the net product of these reactions, i. e., the secretory process, would be a slightly hypertonic fluid whose chief electrolyte constituent would be sodium bicarbonate, and he pointed out that a fluid of this kind does not correspond to the facts, so that his description of the secretory mechanism cannot be complete. Moreover, Friedenwald, on the basis of the available chemical information, stated the belief that the chloride-bicarbonate ratio of the intraocular fluid was approximately the same as that of the plasma and suggested that ionic exchange converts the secreted fluid to one corresponding to aqueous humor.

In the following section, these and other problems related to the secretory mechanism of the ciliary body will be partially resolved.

INTERRELATIONS

Investigations of the composition of aqueous humor relative to that of plasma revealed that certain anions, bicarbonate in particular, exist in significantly higher concentration in aqueous humor than in plasma. The concentrations of other anions, however, such as chloride, are lower in aqueous humor than in plasma. Thus, the chloride-bicarbonate ratio of aqueous humor and that of plasma are not the same, being 3.2 and 4.4, respectively. Studies of the dynamics of aqueous humor in the anterior chamber showed that substances enter and leave this chamber by two processes (diffusion and flow). Studies of the mechanism of secretion in the ciliary body indicated that, as a result of metabolic processes, excess hydroxyl ions are produced in the epithelium and excess hydrogen ions are formed in the stroma. The results of these investigations illustrate well the dynamic nature of the processes leading to the "production" of aqueous humor. The remainder of this paper will be devoted to relating the data presented thus far into a unified theory of aqueous humor dynamics and to an explanation of the maintenance of intraocular pressure.

Friedenwald's hypothesis that hydroxyl ions in the epithelium of the ciliary body are buffered by carbon dioxide, with the formation of bicarbonate, would seem to account readily for the production of bicarbonate in concentrations greater in aqueous humor than in plasma. However, since bicarbonate is in reversible equilibrium with carbon dioxide, a substance that is known to diffuse rapidly through cell membranes, how, with any probable secretory rate, can the concentration of bicarbonate be maintained significantly greater in aqueous humor than in plasma? This question would be resolved if the concentration of carbon dioxide in aqueous humor is less than in plasma. Since the carbon dioxide–bicarbonate ratio is an inverse function of the p_H of a solution, the p_H of the aqueous humor would necessarily have to be higher than that of the plasma for there to be a lower

TABLE 2.—*Relative p_H and Distribution of Carbon Dioxide, Expressed in Millimoles per Kilogram of Water, in the Aqueous Humor and Plasma of Rabbits*

Aqueous Humor					Plasma				
Eye	p_H	Total CO_2	HCO_3^-	CO_2 as H_2CO_3	p_H	Total CO_2	HCO_3^-	CO_2 as H_2CO_3	CO_2 (Plasma — Aqueous)
OD	7.52	35.2	33.9	1.3	Arterial 7.38	28.8	27.4	1.5	0.2
OD	7.52	33.3	32.1	1.2	Venous 7.36	30.7	29.1	1.5	0.3
OD	7.56	32.5	31.4	1.1	Venous 7.40	29.6	28.2	1.4	0.3
OS	7.54	....	....	...					
OD	7.61	35.6	34.2	1.4	Arterial 7.42	31.0	29.6	1.4	0
OS	7.56	....	....	...					
OD	7.59	35.1	33.9	1.2	Venous 7.42	31.6	30.4	1.4	0.2
OS	7.56	....	....	...					
OD	7.60	....	....	...	Venous 7.41	....	....	...	...
OD	7.61	....	....	...	Arterial 7.42	....	....	...	...
Av.	7.57	34.3	33.1	1.24	7.40	30.4	28.9	1.44	0.20

concentration of carbon dioxide in the aqueous humor than in plasma. To test this possibility, I determined the p_H of samples of aqueous humor and plasma withdrawn approximately simultaneously from rabbits, under conditions that would conserve the carbon dioxide. The method gives values reproducible to a p_H of 0.02. The total carbon dioxide content of the same samples of aqueous humor and plasma was also determined. Results of the experiments, along with the partial pressures of carbon dioxide, are shown in table 2. The latter were calculated by means of the Henderson-Hasselbalch equation.

The average p_H of aqueous humor was 0.17 higher than that of plasma, the values being 7.57 [16] and 7.40 (table 2). In no instance

16. The p_H of aqueous humor found by von Sallmann and Di Grandi (Hydrogen Ion Concentration of the Aqueous, Arch. Ophth. **35**:643 [June] 1946), using an electrometric method, was 7.53; they did not make comparative measurements with plasma.

was the p_H of aqueous humor less than 0.11 higher than that of plasma. The partial pressure of carbon dioxide in aqueous humor (table 2, column 10) was lower than that of the blood (because of the greater alkalinity), despite the greater concentration of total carbon dioxide in the former fluid. The difference in concentration of available carbon dioxide amounted to 0.2 millimole per kilogram of water. Thus, there is a concentration gradient of carbon dioxide from the blood to the aqueous humor. This observation explains why the excess bicarbonate in aqueous humor is not lost rapidly by back diffusion of carbon dioxide to the blood, and also accounts for a source of carbon dioxide for conversion to bicarbonate in the epithelium. Moreover, the difference in p_H between aqueous humor and plasma would seem to represent direct experimental evidence for Friedenwald's theory that excess hydroxyl ions are being produced in the epithelium of the ciliary body, since it would seem essential for his theory that the p_H be higher in aqueous humor than in plasma.

The production of hydroxyl ions, with subsequent conversion to bicarbonate ions, however, is, in itself, inadequate to account for aqueous humor as it is found in the anterior or the posterior chamber, since, as Friedenwald concluded, such a process would lead only to the production of a slightly hypertonic fluid consisting of basic bicarbonate (chiefly sodium bicarbonate). Other mechanisms, therefore, must also be involved in the production of aqueous humor. These mechanisms, together with the process responsible for producing bicarbonate ions, must account for a hypertonic aqueous humor in which the nonmetabolized nonelectrolytes and anions (other than bicarbonate, ascorbate and lactate) exist in concentrations less than in plasma.[17] These mechanisms must also account for relative deficiencies of cations, such as calcium and perhaps potassium, in aqueous humor.

I believe that these characteristics of aqueous humor can be accounted for on the assumption that all constituents of plasma can diffuse between the blood of the ciliary body and the fluid in the posterior chamber (through the capillary endothelium, stroma, barrier and epithelium). Since there is little or no experimental evidence concerning the transfer of various substances from the blood to the posterior chamber, it is necessary to theorize as to the probable nature of the fluid which would result from the assumption that all substances can diffuse into and out of the posterior chamber, and that, superimposed on this process, bicarbonate ions are manufactured as a result of oxidation of metabolites by the epithelium and stroma of the ciliary body. This hypothesis would lead to the interstitial fluid of the stroma being slightly hypotonic and of slightly lower p_H than plasma; but,

17. After correction for the Gibbs-Donnan effect.

because of the abundant blood supply of this tissue, these differences would be minimal.

All the diffusional processes and the secretory mechanism (production of bicarbonate ions) occur simultaneously; however, the nature of the resultant fluid can be better understood perhaps by consideration of the movement of the individual constituents. As an aid in visualization of the movement of these constituents, a schematic chart (fig. 3) has been prepared in which the net gain of each substance is represented by the solid arrowheads and those aspects more directly concerned with the secretory process are represented by the greater density of the lines.

The conversion of carbon dioxide to bicarbonate in the epithelium and of bicarbonate to carbon dioxide in the stroma are shown in the

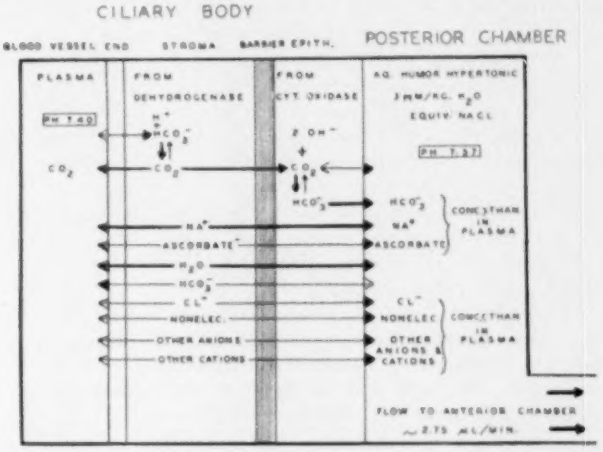

Fig. 3.—Movement of various substances from the posterior chamber to and from the blood.

upper part of the figure. As a result of the imbalance of electric charge on the epithelium,[18] sodium (and other cations) is being transferred continuously into the posterior chamber, thereby maintaining electrostatic neutrality. This transfer leads to a greater concentration of sodium in the aqueous humor as compared with plasma under steady state conditions than would obtain otherwise under equilibrium conditions as a result of diffusional forces alone.

18. It should be observed that while excess positive ions (hydrogen ions) are being produced in the stroma these are converted to nonionic carbon dioxide, which is rapidly lost by diffusion.

It may be argued that loss of a chloride or other anion from the aqueous humor at the time a bicarbonate ion is produced would remove the necessity for the entrance of a neutralizing cation. Because the concentration of chloride is less in aqueous humor than in plasma, there will always be more chloride ions diffusing into the posterior chamber than diffuse in the reverse direction. Therefore, the argument is invalid.

It may be argued also that back diffusion of ions which are in excess in the aqueous humor (sodium, bicarbonate and ascorbate) would prevent this fluid from becoming or remaining hypertonic. Such loss will indeed tend to reduce the hypertonicity, but so long as there is any finite production of bicarbonate as a result of the metabolic process the aqueous humor will always be hypertonic to plasma. The magnitude of the hypertonicity will depend on the relative rates of the metabolic process and the diffusion rate of its end products.

Chloride and other anions, which are assumed to enter the posterior chamber by diffusion, as previously mentioned, exist at steady state in lower concentrations in aqueous humor than in plasma because water, entering the posterior chamber as a result of the hypertonicity created by sodium bicarbonate, acts as a diluent. The magnitude of the deficiency would be expected to differ for each anion, depending on the relative diffusion rates of the ions. These rates depend on mobility, solubility characteristics, and so on. Thus, protein, with an extremely low diffusion rate, exhibits the greatest deficiency. Substances such as sulfate and phosphate, which presumably have diffusion rates between that for chloride and that for protein, will have steady state concentration ratios intermediate between that for chloride and that for protein, viz., about 0.5. For similar reasons, the concentration of nonelectrolytes, at steady state, in the posterior chamber will be less than that in plasma, and the relative deficiency would also be expected to depend on the rates of diffusion. The steady state concentrations of cations in aqueous humor compared with those in plasma, relative to sodium, would be expected to depend also on the relative rates of diffusion. The relative deficiency of potassium, and, particularly, of calcium can be accounted for on this basis.

The transfer of ascorbic acid from plasma to the posterior chamber represents a special case, since the concentration in aqueous humor greatly exceeds that in plasma. Various theories to account for the entrance of this substance into the posterior chamber have been proposed and are discussed elsewhere.[8] Since the absolute concentration of ascorbic acid in aqueous humor is relatively low (less than 0.5 per cent of the total concentration of dissolved substances), this substance would tend to contribute only slightly to the hypertonicity of the aqueous humor and, because ascorbic acid exists chiefly as an anion at body

P_H, would, like bicarbonate, require an additional net transfer of sodium to maintain electrical neutrality.

The excess of lactic acid in the aqueous humor can be accounted for readily by diffusion from the lens, as a by-product of its metabolism, and possibly also from the linings of the anterior segment of the eye. Similarly, the excess of hyaluronic acid in the aqueous humor can probably be accounted for on the basis that it is manufactured by the ciliary epithelium or that it enters from the vitreous humor.

Thus, in conclusion, the hypertonicity of aqueous humor and its composition relative to that of plasma can both be explained chiefly on the basis of the assumption that all constituents of the plasma are capable of diffusing between the blood and the posterior chamber, and on the basis of Friedenwald's proposed mechanism for production of unbalanced bicarbonate ions. However, this concept of aqueous humor "formation" may represent an oversimplification.[19] Consideration must also be given to the possibility that some bulk transfer of substances occurs from the blood to the posterior chamber, perhaps as a result of the electric current set up from the epithelium to the stroma, as suggested by Friedenwald and Stiehler.[14] In designing further experiments, it would seem profitable to attempt to distinguish between unidirectional transfer, as in bulk movement, and to and fro movement, as in the diffusional hypothesis previously described.

Details of the movement of the chief constituents of the plasma into the anterior and posterior chambers of the eye are shown schematically in figures 2 and 3. An over-all picture of the transfer

19. Friedenwald (personal communication to the author) pointed out that my data on water transfer into the eye may indicate a mechanism other than osmotic and diffusional forces involved in transferring water into the eye. He pointed out that the net excess of water transferred into the anterior chamber (2.75 microliters per minute) compared with the total diffusional exchange (47.25 microliters per minute) amounts to approximately 5 per cent, whereas the net excess of diffusional pressure tending to bring water into the eye compared with that tending to remove water is approximately 0.015 per cent. (The total diffusional pressure of water in isotonic saline solution is approximately 55 moles × 22.4 atm. per mole × 760 mm. Hg per atm. = 945,000 mm. Hg, and the excess diffusional pressure is but 150 mm. of mercury). Consequently, he concluded, unless the ratio for net transfer "in" divided by the total exchange is considerably in error, most of the net transfer "in" must be accounted for by some factor other than diffusion. However, he called attention to recent work on fluid exchange in the general vascular system, in which the rate of exchange is very much faster than previously supposed, so much so, in fact, that the limiting factor is the mixing time of the extravascular fluid. It is likely that the estimate of the exchange of water as 50 microliters per minute is also limited by the mixing rate and therefore is really a measure of this rate, rather than of the actual diffusional exchange. In the absence of direct evidence to the contrary, I am inclined to accept this explanation of the apparent discrepancy and believe that diffusional and osmotic forces are sufficient to account for transfer of water into the eye.

of different classes of substances from the blood into and out of the eye, oriented with respect to their anatomic sites of entrance and exit, is represented in figure 4. Bicarbonate is shown separately from the other electrolytes because of the unique pilot role which it apparently plays in dynamics of the aqueous humor.

The movement of various constituents of the aqueous humor in the posterior chamber to and from the vitreous humor is not indicated in the chart because the present paper is primarily concerned with the dynamics of the aqueous humor as it relates to the anterior segment of the eye only.

The only substance shown in the figure to move from the anterior chamber into and out of the cornea is water, since Cogan and Kinsey [20] showed that the endothelium of the cornea is impermeable to electrolytes and has a low permeability to nonelectrolytes unless they possess both water and fat solubility.

The cross section of an eye shown in the figure is that of a human being, whereas the data presented have been obtained from experiments on rabbits. However, recent experiments, which show that the rate of flow of aqueous humor [21] and the rate of movement of water between blood and the anterior chamber of the human eye [22] are essentially identical with those in the rabbit eye, suggest that the dynamics of aqueous humor of the human eye may closely resemble that of the rabbit eye.

MAINTENANCE OF INTRAOCULAR PRESSURE

Knowledge of the mechanism of transfer of various constituents of the plasma into the posterior and anterior chambers of the eye affords a basis from which to evolve a concept for the maintenance of intraocular pressure.

The two kinds of forces available to produce intraocular pressure (on the basis of the foregoing hypothesis) are derived from the hydrostatic and the osmotic pressure. The hydrostatic pressure is derived from the capillary pressure; it has been estimated by Duke-Elder [23] to amount to approximately 50 mm. of mercury. The osmotic pressure is derived from the difference in concentration of all dissolved substances in aqueous humor and plasma; it has been shown to correspond to 3 millimoles per kilogram of water equivalent of sodium chloride.[3] This

20. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, Arch. Ophth. **28**:661 (Oct.) 1942.

21. Goldmann, H.: Der Uebertritt von Fluorescein aus dem Blut ins Kammerwasser des normalen Menschen, Experientia **5**:295, 1949.

22. Cagianut, B.; Heusser, H., and Eichenberger, K.: Beitrag zum Wasseraustausch zwischen Kammerwasser, Linse und Glaskörper beim Menschen, Experientia **5**:243, 1949.

23. Duke-Elder, W. S.: The Ocular Circulation: Its Normal Pressure Relationships and Their Physiological Significance, Brit. J. Ophth. **10**:513, 1926.

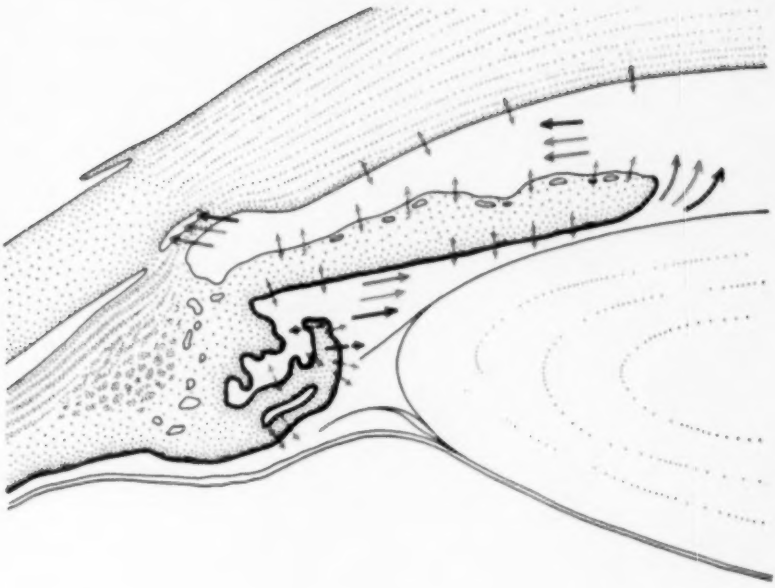

Fig. 4.—Movement of different classes of substances from the blood into and out of the eye. (Bicarbonate is shown separately from the other electrolytes because of the unique pilot role that it apparently plays in dynamics of the aqueous humor).

difference in concentration, under suitable conditions, could give rise to an osmotic pressure of 100 mm. of mercury. Since both these forces

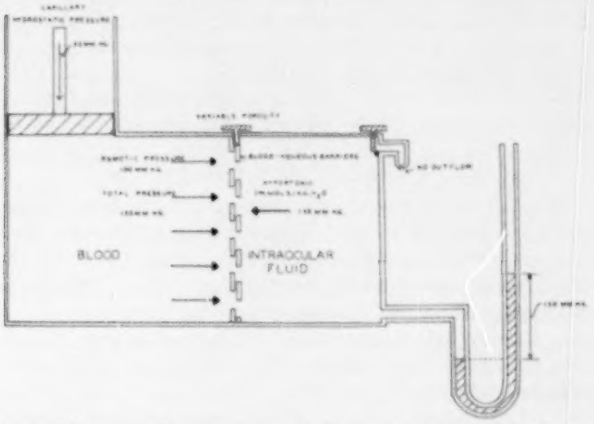

Fig. 5.—Diagrammatic representation of the pressure relations existing between blood and the intraocular fluid in the absence of outflow.

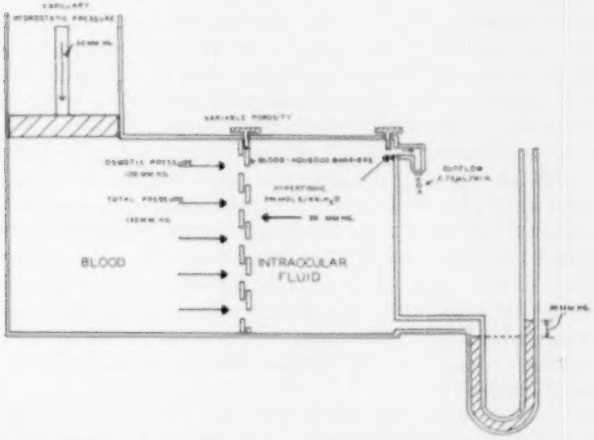

Fig. 6.—Diagrammatic representation of the pressure relations existing between blood and the intraocular fluid in the presence of outflow.

are in the direction of blood to intraocular fluid, in a closed system they could give rise to a pressure of approximately 150 mm. of mercury. This situation is shown diagrammatically in figure 5. However, the eye

is not a closed system, but contains a structure at the angle that permits outflow of intraocular fluid. This outflow reduces the effectiveness of the forces that transfer water into the posterior and anterior chambers, so that the actual intraocular pressure (in rabbits) is only about 30 mm. of mercury. A diagrammatic representation analogous to the situation in the eye is shown in figure 6.

The following simplified schema has been found useful in teaching students the relation of the factors responsible for the intraocular pressure.

$$IOP = K\,[(OP_{Aq} - OP_{Pl}) + Cap\ P] \qquad (1)$$

OP_{Aq} and OP_{Pl} represent osmotic pressure of the aqueous humor and plasma, respectively, and Cap P represents capillary pressure. Friedenwald [12] suggested that the independent contribution of the factors tending to move water into and out of the eye can be better expressed by substituting for K the expression $\frac{k_{in}}{k_{in} + k_{out}}$ where k_{in} and k_{out} represent the effectiveness with which the osmotic and hydrostatic forces are converted into intraocular pressure. This relationship and its derivation follow.

$$\begin{aligned} k_{out} \cdot IOP &= k_{in}\,[(OP_{Aq} - OP_{Pl}) + (Cap\ P - IOP)] \\ &= k_{in}\,[OP_{Aq} - OP_{Pl} + Cap\ P] - k_{in} \cdot IOP \\ IOP &= \frac{k_{in}}{k_{in} + k_{out}}\,[OP_{Aq} - OP_{Pl} + Cap\ P] \qquad (2) \end{aligned}$$

The fraction $\frac{k_{in}}{k_{in} + k_{out}}$ varies between the limits of zero and 1. When k_{out} is infinite, as after surgical procedures, the fraction is zero; when the outflow is obstructed, as in glaucoma, the fraction is 1. The fraction can be evaluated for a normal eye by substituting known values in the schema representing intraocular pressure. For the rabbit eye this fraction has a value of 0.2 (30 mm. Hg = $\frac{k_{in}}{k_{in} + k_{out}}$ (100 mm. Hg + 50 mm. Hg). For the human eye, which has an intraocular pressure of 20 mm. of mercury, a difference in osmotic pressure corresponding to 5 millimoles per kilogram of water equivalent of sodium chloride,[24] or approximately 170 mm. of mercury, and a capillary pressure of approximately 50 mm. of mercury, $\frac{k_{in}}{k_{in} + k_{out}}$ is equal to approximately 0.1. Thus, in a human eye the change in intraocular pressure would be only about 10 per cent of any change in the difference in osmotic pressure between aqueous humor and plasma, or in the capillary pressure.

In general, if k_{in} and k_{out} increase in the same proportion, the fraction (K) is unchanged; and if, as one would expect as a first approximation, $OP_{Aq} - OP_{Pl}$ varies inversely with k_{in}, the intraocular pressure will decrease. If k_{out} remains stationary or falls while k_{in}

24. Hodgson, T. H.: Studies on the Aqueous Humour in Normal and Glaucomatous Eyes, Tr. Ophth. Soc. U. Kingdom **58**:87, 1938.

rises and if OP_{Aq}—OP_{Pl} falls inversely with k_{in}, then the intraocular pressure will rise.

The magnitude of the difference in the osmotic pressure of aqueous humor and of plasma depends chiefly on the rate of production of bicarbonate and ascorbate ions, i. e., the rate of secretion, and the degree of impermeability of the blood-aqueous barriers to back diffusion. The magnitude of the capillary pressure, presumably, is directly or indirectly related to the blood pressure.

Any theory designed to account for the maintenance of normal intraocular pressure must also be able to account for changes in intraocular pressure resulting from disease or experimentally induced alterations in the blood. The present concept, as shown later, can account for many of these changes.

The schema presented here illustrates the importance of the resistance of outflow (k_{out}) in determining intraocular pressure. This conclusion is consistent with the well known rise in intraocular pressure following blockage of the angle, as in glaucoma. Moreover, the schema permits quantitative evaluation of the effect of any decrease in patency of the angle of the rabbit's eye or of Schlemm's canal in the human eye, provided the k_{in} factors are known or remain unchanged.

An increase in the permeability of the blood-aqueous barriers (k_{in}), such as, for example, that following inflammation of the uveal tract, might result in no change in intraocular pressure, an increase in pressure or a decrease in pressure, depending on whether there is a concomitant change in the ease of outflow (k_{out}). For example, if the permeability of the blood-aqueous barrier increases without change in ease of outflow, the intraocular pressure would be expected to increase slightly, whereas if the inflammation also results in an increase in the ease of outflow, the pressure might actually decline. The operation of these two independent mechanisms controlling pressure readily explains some of the contradictory observations with regard to changes in pressure resulting from inflammation.

An interesting example of change in pressure following iritis was called to my attention by Dr. Paul Chandler, who treated a patient having an intraocular pressure of about 40 mm. of mercury. Iritis developed, and the intraocular pressure decreased to 20 mm. of mercury, where it remained until remission of the iritis. The pressure then rose to 40 mm. of mercury. Subsequently, the same cycle of alterations in pressure occurred when iritis again developed.

There is a lack of correlation between the intraocular pressure and the colloid osmotic pressure of the blood. For example, Robertson [25]

25. Robertson, J. D.: Some Observations on Fluid Interchange and Its Bearing on Certain Ophthalmological Problems, Tr. Ophth. Soc. U. Kingdom **58**:75, 1938.

observed that patients with nephrosis, whose colloid osmotic pressure was reduced from 30 mm. to approximately 15 mm. of mercury, had normal intraocular pressures.

On the basis of the present hypothesis, a change in colloid osmotic pressure of 15 mm. of mercury (in the absence of other changes) would give rise to a change in intraocular pressure of less than 1.5 mm. of mercury, a variation not readily perceptible by ordinary clinical methods for determining intraocular pressure and well within normal daily fluctuation.

Intraocular pressures above the capillary pressure and, more rarely, momentary pressures higher than the arterial pressure of the eye have been observed in patients with glaucoma. Pressures of this kind, which could not be accounted for by earlier views of the mechanism of the maintenance of intraocular pressure, are readily explainable by the present theory, since, as previously observed, forces available to bring water into the eye of a human being are theoretically capable of giving rise to a pressure of the order of 200 mm. of mercury.

Thus far, factors leading to sustained changes in the intraocular pressure have been considered. Transient changes also conform to the general schema for explaining intraocular pressure. For example, increase in intraocular pressure following intake of large amounts of water, as in one of the provocative tests for glaucoma, results from increasing the difference in osmotic pressure between aqueous humor and plasma. Alterations in intraocular pressure from this cause are transitory and eventually lead to a momentary decrease in intraocular pressure below normal levels. Similarly, the intravenous administration of sugar, or exercise, decreases the difference in osmotic pressure between aqueous humor and plasma, resulting in a decrease in intraocular pressure.

In conclusion, both the normal intraocular pressure and the many alterations in intraocular pressure associated with disease or induced experimentally can be accounted for, at least qualitatively, by the proposed theory.

SUMMARY

A unified concept of the dynamics of the aqueous humor which can account for the relative concentration of the constituents of this fluid as compared with that of plasma, and also for the intraocular pressure of normal eyes and eyes showing various pathologic conditions, is presented.

This concept, as it relates to the movement of constituents of the plasma into the posterior chamber, involves the production of unbalanced hydroxyl ions, as suggested by Friedenwald, and the simultaneous diffusion of all the constituents of the plasma into and out of the posterior chamber. The hydroxyl ions, by reaction with carbon

dioxide, are converted to bicarbonate ions, which are electrically neutralized by sodium and other cations diffusing from the blood. The salts formed diffuse into the posterior chamber, thereby maintaining the aqueous humor hypertonic to the plasma. As a result of this hypertonicity, more water diffuses into the posterior chamber than diffuses out again; i. e., there is a net transfer of water into the posterior chamber. The excess transfer of water into the posterior chamber dilutes the other substances which are diffusing to and fro between the blood and the posterior chamber, so that, at steady state, they exist in lower concentration in the aqueous humor than in the plasma. The aqueous humor thus "formed" flows between the iris and the lens into the anterior chamber, where there is a further exchange of nonelectrolytes along with a major exchange of water across the iris. The electrolytes do not exchange, however, because the walls of the blood vessels of the iris are impermeable to ions under normal conditions. All the constituents of the aqueous humor of the anterior chamber then escape by flow from the eye at the angle at a rate of about 3 microliters per minute. The influx of water as a result of hydrostatic and osmotic pressures, particularly the latter, is responsible for the intraocular pressure. The magnitude of the pressure depends on the rate of production of hydroxyl ions in the epithelium of the ciliary body, the ease of outflow at the angle and, to a less extent, the porosity of the blood-aqueous barriers. Under normal conditions these factors are in balance. Under abnormal conditions they may vary independently and give rise to either an increase or a decrease in intraocular pressure.

This concept is based on evidence derived from previously published experimental studies on the rabbit and on new experimental evidence in support of the production of excess hydroxyl ions in the epithelium of the ciliary body. This new evidence consists of the demonstration that the p_H of the aqueous humor exceeds that of the plasma by 0.17.

Certain sustained and transient alterations in intraocular pressure resulting from disease or induced experimentally are discussed in the light of the theory proposed to account for the maintenance of intraocular pressure.

Drs. Malcolm Holliday and William Wallace, of the Children's Hospital, Boston, assisted in performing the determinations of the p_H.

OCULAR FINDINGS IN THE NEWBORN INFANT

A Preliminary Report

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AND

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NEW YORK

RECENTLY Babies Hospital, of the Columbia-Presbyterian Medical Center, has undertaken a comprehensive program of study in the field of diseases of infants associated with birth. This study will extend over a period of years. Working with the staff of the Babies Hospital are members of various departments of the medical specialties. The purpose of this paper is to consider the incidence of ocular disease in the newborn infant, with special emphasis on the study of the ocular fundus.

In the course of this study we were surprised to find that the incidence of retinal hemorrhage following birth was 2.6 per cent. This is in conflict with most reports in the literature of the past few years. Thus, Vancea [1] saw retinal hemorrhages in 50 per cent of his cases, and McKeown [2] reported an incidence of 42.1 per cent. Wille [3] observed retinal hemorrhages in 42.4 per cent, and Falls and Jurow,[4] in 32.4 per cent.

When these figures are compared with the 2.6 per cent found in the present study, one wonders what factor has entered the picture.

This investigation is being aided by grants from the Rockefeller Foundation, the Life Insurance Medical Research Fund and the Snyder Ophthalmic Fund.

From the Departments of Ophthalmology, Pediatrics and Obstetrics, Columbia University College of Physicians and Surgeons; the Institute of Ophthalmology; Babies Hospital, and Sloane Hospital for Women.

1. Vancea, P.: Die Netzhautblutungen des Neugeborenen, Klin. Monatsbl. f. Augenh. **107**:272-280 (Sept.) 1941.

2. McKeown, H. S.: Retinal Hemorrhages in the Newborn, Arch. Ophth. **26**:25-37 (July) 1941.

3. Wille, H.: Investigations in the Influence of Vitamin K Avitaminosis on the Occurrence of Retinal Hemorrhages in the Newborn, Acta. ophth. **22**:261-269, 1944.

4. Falls, H. F., and Jurow, H. N.: Effect of Antepartum Vitamin K on Retinal Hemorrhage, J. A. M. A. **131**:203-205 (May 18) 1946.

Dr. Frederick Blodi,[5] of the staff of the Institute of Ophthalmology, who has continued the study, informed us in a personal communication that of 469 newborn infants examined by him, hemorrhages were found in 17, or only 3.6 per cent.

It is of interest to note that vitamin K therapy is not administered to mothers in labor as a matter of routine at the Sloane Hospital, and that it is withheld from the babies except for premature infants and infants who present evidence of hemorrhage. During the early part of the past decade it was strongly believed that the administration of some form of vitamin K to the mother during the latter part of pregnancy or at the time of labor would prevent the tendency to retinal hemorrhages and other hemorrhagic manifestations by raising the prothrombin level. Thus, Pray, McKeown and Pollard,[6] in 1941, reported a reduction of retinal hemorrhages to 13 per cent, supposedly as the result of the use of vitamin K. They also found that formula feeding rather than breast feeding had the same effect. Maumenee, Hellman and Shettles,[7] in 1941, found that retinal hemorrhages were reduced to 4 per cent after the use of vitamin K. Menadione U. S. P. (2 methyl-1, 4-naphthoquinone), 2 mg. in tablet form, was given three times a day to the mother for periods varying from three days to six weeks before delivery. Waddell and Lawson[8] reported the routine use of the same material for the last ten days of pregnancy; in addition, they gave 0.5 cc. to the infant immediately after birth. Poncher and Kato[9] and Quick and Grossman[10] stated the belief that the general tendency to hemorrhagic disease in the newborn would be reduced by this prenatal therapy. Sanford, Shmigelsky and Chapin,[11] however, in a careful study, found

5. Blodi, F.: Personal communication to the authors.

6. Pray, L. C.; McKeown, H. S., and Pollard, W. E.: Hemorrhagic Diathesis of the Newborn: Effect of Vitamin K Prophylaxis and Therapy, Am. J. Obst. & Gynec. **42**:836-845 (Nov.) 1941.

7. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infant: IV. The Effect of Antenatal Administration of Vitamin K on the Incidence of Retinal Hemorrhage in the Newborn, Bull. Johns Hopkins Hosp. **68**:158-186 (Feb.) 1941.

8. Waddell, W. W., Jr., and Lawson, G. M.: Hemorrhagic Diathesis of the Newborn: Further Observations Concerning Prevention and Treatment, J. A. M. A. **115**:1416-1421 (Oct. 26) 1940.

9. Poncher, H. G., and Kato, K.: Treatment of Hypoprothrombinemia Haemorrhagica Neonatorum (Hemorrhagic Disease of the Newborn) with Vitamin K, J. A. M. A. **115**:14-17 (July 6) 1940.

10. Quick, A. J., and Grossman, A. M.: The Nature of the Hemorrhagic Disease of the Newborn: Delayed Restoration of the Prothrombin Level, Am. J. M. Sc. **199**:1-9 (Jan.) 1940.

11. Sanford, H. N.; Shmigelsky, I., and Chapin, J. M.: Is Administration of Vitamin K to the Newborn of Clinical Value? J. A. M. A. **118**:697-702 (Feb. 28) 1942.

that the incidence was not in the least affected by giving vitamin K to the mother. The percentage of hemorrhagic disease (not including retinal hemorrhage) was 6.5 per cent for the infants of treated mothers and 6.6 per cent for the infants of untreated mothers.

At the Sloane Hospital, prior to 1945 vitamin K in the form of menadione sodium bisulfite U. S. P. (hykinonen®; 2 methyl-1, 4 naphthohydroquinone-3 sodium sulfonate) was given parenterally, in a single injection of 1 cc., as routine treatment to mothers. After 1945 this routine was abandoned, largely owing to the work of Potter.[12] She studied 13,000 infants, half of whom were born of mothers receiving menadione sodium bisulfite, in the amount of 3.2 mg., on admission to the labor room. She concluded that "in a carefully controlled group of infants anything which can be considered hemorrhagic disease is extremely rare" and that "the influence of the hemorrhages which do occur in this age group is not modified by administration of vitamin K to the mother prior to delivery or to the infant after birth." Falls and Jurow [4] found that their incidence of retinal hemorrhage was not altered by similar therapy.

Vigorous manual technics of resuscitation have been abandoned in the obstetric service. Infants who have serious difficulty in breathing are given oxygen immediately. However, manual resuscitation in the form of gentle body massage is still practiced to aid respiration.

METHOD OF STUDY

In this study, all mothers who presented themselves at the Sloane antepartum clinic within the first four months of their pregnancy were included in the series. A total of 1,268 infants in this group were delivered between Jan. 1, 1947 and May 19, 1948, the period covered by this report. Infants were examined, so far as possible, on the day of birth or a few days afterward. In some cases, owing to the child's physical condition, five or six days passed before examination. No examination was made of 98 infants, owing to various circumstances; in addition, 19 infants died before they could be seen. This brought the total series to 1,151.

Before the infants were seen, the pupils were dilated with 0.5 per cent homatropine hydrobromide. The solution was instilled about one hour before the ophthalmologist arrived. Usually dilation was quite satisfactory. The baby was then placed on a table and restrained by a nurse while the physician observed the external portion of the eyes and studied the fundus. No anesthesia was used, nor was it considered advisable. As a result, the eyes were usually in constant motion. However, a good view of the fundus could be obtained in most instances. The same technic of examination was used by McKeown,[2] who, as already noted, found hemorrhages in 42.1 per cent of the infants examined, as compared with our figure of 2.6 per cent.

12. Potter, E. L.: The Effect on Infant Mortality of Vitamin K Administered During Labor, Am. J. Obst. & Gynec. **50**:235-247 (Sept.) 1945.

ANALYSIS OF MATERIAL

Table 1 shows that, of 1,151 infants, blepharospasm occurred in 127, or 11.0 per cent, making a total of 1,024 in whom the external eye could be observed adequately. Esotropia was found in 2, or 0.2 per cent; exotropia in 18, or 1.8 per cent, and cataracts of polar type in 4, or 0.4 per cent. In no instance was retrolental fibroplasia noted, although the children were followed for over a year. There was no history of measles or rubella in the mothers.

In table 2 the appearance of retinal hemorrhages is considered in relation to prematurity. Of 1,151 infants, the fundus could be seen

TABLE 1.—*Findings on External Examination of Eyes*

Total number of infants examined		1,151
Number with blepharospasm	127, or 11.0%	
Total number of infants whose eyes were examined externally		1,024
Esotropia	2 (0.2%)	
Exotropia	18 (1.8%)	
Cataract	4 (0.4%)	

TABLE 2.—*Relation of Retinal Hemorrhages to Prematurity*

Total number of infants examined		1,151
Number with fundus seen adequately	839, or 72.9%	
Number with retinal hemorrhage	22, or 2.6%	
Number of term infants studied		773
Number with hemorrhage	19, or 2.5%	
Number of premature infants studied		66
Number with hemorrhage	3, or 4.5%	

adequately in only 839, or 72.9 per cent of the total. The data on the remainder were discarded as unsatisfactory. Of the 839 infants accepted for study, only 22, or 2.6 per cent, showed retinal hemorrhages. These were flame shaped in 16 infants and were often multiple and usually just adjacent to the vessels near the optic disk. Of round, pin-point hemorrhages there were 6 instances. Of the 839 infants whose fundi were adequately seen, 773 were term babies, and 19, or 2.5 per cent, were affected. The remaining 66 infants were premature, and of these, 3, or 4.5 per cent, had retinal hemorrhages.

Table 3 shows that, in general, infants examined within the first three days after birth showed a higher incidence of retinal hemorrhage (4.5 per cent) than those examined later (1.4 per cent). In view of McKeown's [2] finding that the small, flame-shaped hemorrhages tended

to be absorbed within two to five days, we may assume that the incidence of hemorrhages in the entire group would have been somewhat higher if all the infants had been examined on the day of birth or within forty-eight hours after birth.

Table 4 shows that the percentage of hemorrhages was apparently higher in cases of forceps delivery, an observation in line with the theory held by many that retinal hemorrhages of the newborn infant are related to the trauma of birth. Statistical analysis, however, reveals that the difference is not significant and could be a matter of chance.

TABLE 3.—*Relation of Hemorrhages to Time of Examination After Birth*

Time of Examination	Number of Patients Examined	Patients with Hemorrhages	
		No.	Per Cent
Day of birth	25	2	8.0
1st	119	4	3.4
2nd	186	9	4.8
3rd	125	1	0.8
4th	145	2	1.4
5th	120	2	1.7
6th	96	2	2.1
7th	18	0	0.0
8th	5	0	0.0
Total	839	22	2.6

TABLE 4.—*Relation of Retinal Hemorrhages to Trauma at Birth*

Total number of infants with fundus seen adequately		839
Spontaneous delivery	627	
Hemorrhages	13, or 2.1%	
Forceps delivery	178	
Hemorrhages	9, or 5.1%	
Cesarian section	34	
Hemorrhages	0, or 0.0%	

Sex apparently makes no difference in the frequency of retinal hemorrhages, as hemorrhages occurred in 12 male and in 10 female infants.

During the period covered by the study there were 30 stillbirths. Of these stillborn babies, 18 had complete pathologic study of the eyes. Retinal hemorrhages were observed in 2 and hemorrhages in the optic nerve in 1 (figs. 1 and 2).

SUMMARY

The eyes of a large number of newborn infants were studied immediately after birth. Of 1,024 infants, cataract was found in 4, or 0.4 per cent. No case of retrolental fibroplasia was noted. There was no history of measles or rubella in the mothers of infants showing cataracts.

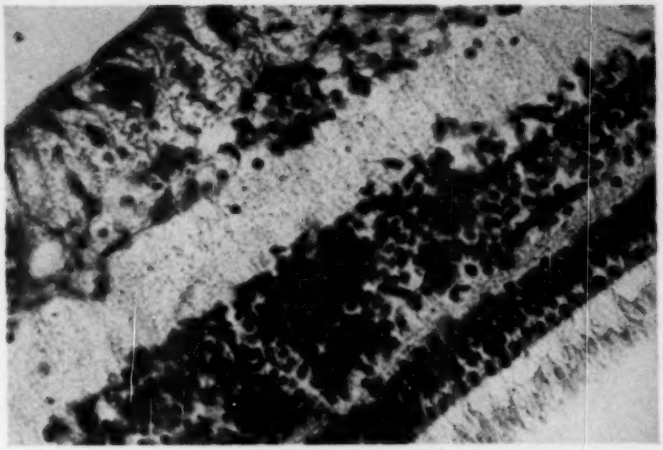

Fig. 1.—Hemorrhage in the retina

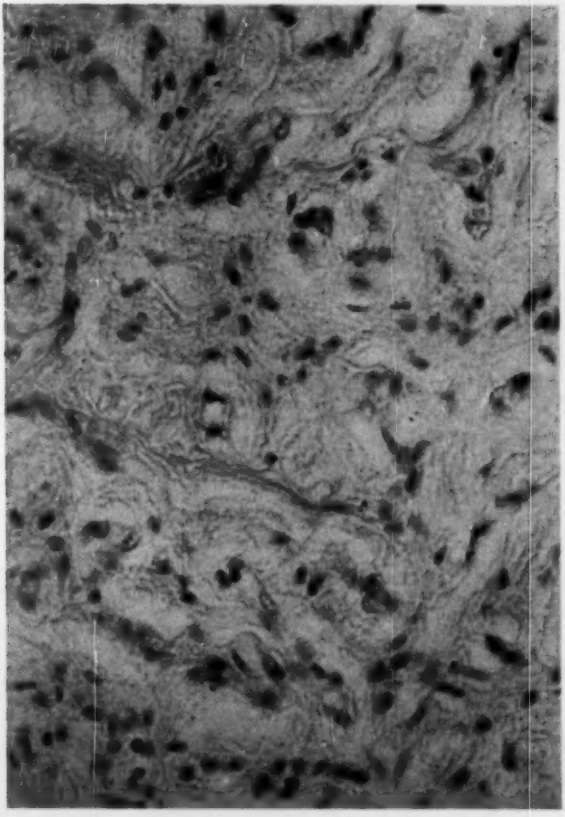

Fig. 2.—High power view of the optic nerve, showing hemorrhage.

Retinal hemorrhages were found in 2.6 per cent of all infants studied. They were most commonly noted shortly after birth.

Further studied are planned to relate the findings to various medical factors in the mother.

Dr. Marion Laird, of the staff of the Sloane Hospital for Women, cooperated in this study; Dr. Gordon M. Bruce, of the staff of the Institute of Ophthalmology, helped in examining some of the infants, and Dr. Beryl H. Paige, of the Department of Pathology of Babies Hospital, made the pathologic studies.

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CERVICAL SYMPATHECTOMY IN NONSYPHILITIC INTERSTITIAL KERATITIS WITH VESTIBULOAUDITORY SYMPTOMS

Report of a Case

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IN 1945 Cogan [1] described the syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms in 4 cases and later [2] reported 4 additional cases. Rosen [3] reported a similar case occurring after vaccination. A search of the literature reveals only 1 other case, reported in 1934 by Moran and Baumgartner.[4] They considered their case to be one of "Ménière's disease complicated by interstitial keratitis," and reported improvement following cervical ganglionectomy. Cogan [2] stated that it is "questionable" whether Moran and Baumgartner's case belongs to this group.

The syndrome consists of predominantly bilateral keratitis running a chronic course, the severity varying from day to day and from eye to eye. The vestibuloauditory symptoms are typically severe vertigo, tinnitus, nystagmus and progressive deafness. The course of the disease, the absence of a familial history and the consistently negative serologic reactions are important parts of the syndromes.

Moran and Baumgartner reported dramatic recovery following bilateral cervical sympathectomy. One of Cogan's [1] patients underwent unilateral cervical sympathectomy, without improvement. It is noteworthy also that 1 of Cogan's patients made a spontaneous recovery. There is much to suggest an inflammatory basis for the condition,[5] possibly due to a virus.

It is the purpose of the present paper to record the eleventh known case of this disease and to report that bilateral cervical sympathectomy was without benefit. Thus, of 11 known cases, sympathectomy has been

1. Cogan, D. G.: Syndrome of Nonsyphilitic Keratitis and Vestibuloauditory Syndrome, Arch. Ophth. **33**:144-149 (Feb.) 1945.

2. Cogan, D. G.: Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms, Arch. Ophth. **42**:42-49 (July) 1949.

3. Rosen, E.: Interstitial Keratitis and Vestibuloauditory Symptoms Following Vaccination, Arch. Ophth. **41**:24-31 (Jan.) 1949.

4. Moran, R. F., and Baumgartner, C. J.: Ménière's Disease Complicated by Recurrent Interstitial Keratitis: Excellent Result Following Cervical Ganglionectomy, West. J. Surg. **42**:628-631 (Nov.) 1934.

5. Cogan.[2] Rosen.[3]

performed in 3, with reported benefit in only 1, the first, and "questionable," case. It was, and is, my belief that this procedure is contraindicated and is without rationale.

REPORT OF CASE

J. M., an attorney aged 27, was seen for the first time on Feb. 11, 1949. He stated that in November 1948 there developed objective vertigo and bilateral high-pitched tinnitus. Severe bilateral impairment of hearing developed and slowly cleared. In the latter part of January 1949 a similar episode occurred, accompanied with conjunctivitis and photophobia. At this time the neurologic and general physical examinations revealed nothing significant. Routine laboratory work, including a blood count, urinalysis and serologic tests, and agglutination tests for Brucella and the typhoid-paratyphoid group were noncontributory. The spinal fluid was normal. An audiogram revealed pronounced impairment of hearing for all frequencies. Caloric tests revealed no response on the left and minimal response on the right. Examination of the eyes revealed inflammation of the bulbar conjunctiva, swelling of the corneal epithelium and clouding of the anterior chamber. The patient was referred to the Mayo Clinic and later was seen at the University of Chicago Clinics. Examinations at these institutions confirmed our own observations.

The hearing loss continued, and the severity of the conjunctivitis varied from time to time and from one eye to the other. Treatment with antibiotics and histamine was ineffective.

In December 1949 the patient came to my office with a copy of the article by Moran and Baumgartner on cervical sympathectomy in treatment of this condition and requested the operation. The procedure was discussed and decided against on the basis of Cogan's experience in 1 case and because recent work has suggested a virus as a causal agent.

The patient was insistent, however, and persuaded another physician, Dr. Flotow, to carry out bilateral cervical-thoracic sympathectomy. On December 16, the middle and inferior cervical and the first and second thoracic sympathetic ganglions were resected on the left side, and on December 21 the same procedure was carried out on the right. Comparison of the ganglions with normal ganglions histologically revealed no abnormal changes.

No change followed the operative procedure except for a transitory increase in the conjunctivitis. In February 1950 he wrote that he was then taking "electrical treatments that dissolved crystals in the eyes" and that "they found the same crystals in the blood stream." A Horner syndrome was present, with the resulting impaired appearance, facial discomfort and ocular hyperemia.

SUMMARY

The eleventh known case of Cogan's syndrome (nonsyphilitic interstitial keratitis with vestibuloauditory symptoms) is reported. Cervical sympathectomy was without benefit.

RETROLENTAL FIBROPLASIA AS A SYNDROME

Pathogenesis and Classifications

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RETROLENTAL fibroplasia is a name applied by Terry [1] in 1942 to a mass of vascular embryonic connective and retinal tissues observed behind the lens in eyes of infants of premature birth. Before Terry's time many sporadic cases of fibrosis behind the lens were reported. A great variety of descriptive terms were used, such as vascular cord in the vitreous, pseudoglioma, persistent hyaloid, atypical vitreous, persistent vitreous, fibrosis of the lens, microphthalmos, embryonic fibrous sheath of the lens and congenital retinal folds. There has been no increase in the sporadic forms of retrolental fibrosis. The past decade has shown a remarkable increase in what has been called "retrolental fibroplasia" in infants of premature birth. This increase is proportional to the degree of prematurity and the lowness of the birth weight, and it is selective in its geographic locality. The large group of infants and children with this defect composes about one-half the blind children of preschool age, and the condition thus has become a public health problem.

Terry, as a result of his pioneer studies, made the following generalizations: Retrolental fibroplasia develops largely, if not entirely,

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From the Eye Pathology Laboratory of the Massachusetts Eye & Ear Infirmary.

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1. Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens: I. Preliminary Report, Am. J. Ophth. **25**:203-204 (Feb.) 1942; Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Infants Born Prematurely: III. Studies in Development and Regression of Hyaloid Artery and Tunica Vasculosa Lentis, ibid. **25**:1409-1423 (Dec.) 1942; Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: II. Report of Cases, Arch. Ophth. **29**:36-53 (Jan.) 1943; IV. Etiologic Factors, ibid. **29**:54-65 (Jan.) 1943; Retrolental Fibroplasia in Premature Infants: Further Studies on Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis, ibid. **33**:203-208, 1945; Ocular Maldevelopment in Extremely Premature Infants: Retrolental Fibroplasia; General Consideration, J. A. M. A. **128**:582 (June 23) 1945; Retrolental Fibroplasia, in Levine, S. Z., and others: Advances in Pediatrics, New York, Interscience Publishers, Inc., 1948, vol. 3.

after birth. Its frequency increases with the degree of prematurity. The exciting causes may be the same in a monocular manifestation in a full term baby as in the bilateral involvement of a prematurely born infant. Hereditary factors do not seem to be concerned. The tissue reaction behind the lens is composed of embryonic connective tissue, unlike the fibrous scar present in cyclitic membrane. Separation of the retina occurs through traction of persistent strands of fibrillary vitreous.

Terry suggested that the premature infant is unable to digest and absorb foodstuffs comparable to the nourishment acquired through the placenta and that vitamin deficiencies, due to insufficient digestion and assimilation of foodstuffs, should be suspected. He said that in cases of twinning the weaker infant is more likely to show the fibrosis. He stated the belief that the precocious increase of blood pressure in the prematurely born infant or in the fetus in utero is a causal factor worthy of consideration. He further suggested that hypertrophy of the hyaloid arterial system took place or that fibrillary vitreous persisted and a growth of embryonic connective tissue took place. He deviated from his original concept, in which he asserted that the process was present at birth, and evolved a different explanation of the disease when he saw the condition develop in eyes which previously had been ophthalmoscopically normal. Prior to this he had asserted that the process was present at birth.

In 1946, Reese and Payne [2] concluded from their clinical and pathologic material that the basic process of retrolental fibroplasia consists in persistence of (1) primary vitreous with or without hyperplasia, (2) secondary changes due to hemorrhage, (3) a ruptured lens capsule and (4) glaucoma. These processes, they stated, existed before birth. They mentioned adhesions of the primary vitreous to the inner surface of the retina and commented that the secondary vitreous failed to develop or was sparse. This observation had previously been made by Howard.[3] Reese and Payne expressed the belief that a relation existed between retrolental fibroplasia and hemangioma in the skin.

Krause,[4] in 1946, reported a clinical and microscopic study of 18 cases. He concluded that the disease was neuroectodermal and that mental retardation, microcephalos and hydrocephalus was usually manifest in affected children who survived the age of 4 years. He observed atrophy, gliosis and detachment of the retina. He also noted post-

2. Reese, A. B., and Payne, F.: Persistent and Hyperplasia of the Primary Vitreous, Am. J. Ophth. **29**:1-19 (Jan.) 1946.

3. Howard, Henry: Further Proof of the Vascularity of the Lens and Its Capsule, Brit. Am. J. Med. & Phys. Sc. **2**:150-153, 1851-1852. Howard, H.: A Case Showing Multiple Congenital Abnormalities of the Eye, Tr. Am. Ophth. Soc. **15**:244, 1917.

4. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, Arch. Ophth. **36**:387-444 (Oct.) 1946.

lental fibrous retinal masses and recurrent hemorrhages in the retina and vitreous. Secondary glaucoma and cataract were common. He stated that the secondary pathologic processes distorted the clinical picture and tended to make the eye smaller than normal. He expressed the belief that retrolental fibroplasia was a part of a number of congenital developmental defects.

In 1948, Owens and Owens [5] reported on a clinical study of the early stage of retrolental fibroplasia as seen with the ophthalmoscope. They, like Terry, observed retinal changes and retrolental opacities in an eye which previously had appeared normal. They described early ophthalmoscopic changes, such as congestion, dilatation of retinal vessels and tortuosity, or an angiomatous type of dilatation and tortuosity. They noted retinal elevations at the periphery, generalized retinal edema and discoloration, and in the late stages a vascular vitreous membrane and organization. They stated the opinion that microphthalmos developed after the formation of a complete retrolental membrane, and, since they had seen the disease begin and in some instances reverse, they expressed the belief that the process was not an arrest in growth or an embryonic aberration of fetal structure. These authors also speculated on metabolic disease as a possible cause. They noted some relation to hemangioma of the skin, as reported by Reese and Payne. Hess, Mohr and Bartelme [6] also had pointed out that hemangioma occurred more frequently in premature children than in full term siblings.

Unsworth,[7] in 1948, concluded from his study that retrolental fibroplasia is not congenital and suggested a correlation between anemia and the disease. He distinguished two main types: (1) proliferations from the retina of a vascular tissue in the posterior part of the fundus with abnormal vitreous and (2) failure in development of a condensation of the secondary vitreous at the anterior portion of the periphery with proliferations into it of retinal vessels from unattached portions of the retina, or (3) a combination of the two types.

In 1949, Kinsey and Zacharias [8] reported on the incidence of retrolental fibroplasia in various cities and attempted to make a correlation between incidence and any treatments used. They found no causal relation in the following factors: parity, age of mother, Rh type, type

5. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Am. J. Ophth. **32**:1 (Jan.) 1949.

6. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934.

7. Unsworth, A. C.: Retrolental Fibroplasia: A Preliminary Report, Arch. Ophth. **40**:341 (Sept.) 1948.

8. Kinsey, V. E., and Zacharias, Leona: Retrolental Fibroplasia, J. A. M. A. **139**:572-578 (Feb. 26) 1949.

of delivery, the analgesic and anesthetic used, causes of prematurity, single or multiple births, sex and congenital anomalies. Their over-all conclusions were that there has been an increase in retrolental fibroplasia in recent years and that there exists some correlation between frequency of retrolental fibroplasia and the use of vitamin A supplements (water-soluble form) and of iron in the treatment of children of premature birth. In their studies, they, like Terry, implicated a metabolic disease as being fundamentally at fault.

In 1949 Owens and Owens [9] discussed the problem of the cause of retrolental fibroplasia and in a small series of cases reported the trial of alpha tocopherol as a preventive and therapeutic agent. The basis for this was the use of vitamin E to overcome a depressed level and, presumably, the clinical use of the tocopherols by others in the treatment of primary fibrositis and in experiments with animals.

Reese, in 1949,[10] again emphasized his conception of the maternal causative agent by pointing out the high incidence of maternal bleeding and angiomatous changes seen in the ocular specimens and the skin of premature infants. He reiterated his belief that the matrix of retrolental fibroplasia is present at birth, that in one type the patients show persistence of primary vitreous and hyperplasia of the structures, including the mesenchymal tissue, and that at least two different conditions are confused. In his series the eyes were usually microphthalmic, but some were of normal size. He stated that the lesion can appear in full term infants. According to Reese, the basic lesion is congenital, "the remains of some angiomatous mesoderm from the primary vitreous, and from this tissue hemorrhage occurs, resulting in organization, retinal detachment, with perhaps an element of hyperplasia."

Klien [11] in 1949, reported a series of cases of retrolental fibroplasia and agreed with Reese's position that the matrix of the disease exists at birth. She emphasized that the lesion is angiomatous and that it may be associated with the causes of maternal bleeding. She stated that in her opinion the lesion develops from an "angioblastic overgrowth of the primary vitreous in response to some disturbance as yet unknown."

Owens and Owens,[9] in 1949, reported encouraging results from the use of alpha tocopherol acetate as a preventive if given early, before the

9. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: II. Studies on the Prophylaxis of the Disease; The Use of Alpha Tocopherol Acetate, Am. J. Ophth. **32**:1631 (Dec.) 1949; presented in part at the eighth clinical meeting of the Wilmer Residents Association.

10. Reese, A. B.: Persistence and Hyperplasia of Primary Vitreous: Retrolental Fibroplasia—Two Entities, Arch. Ophth. **41**:527-552 (May) 1949.

11. Klien, B.: Histopathologic Aspects of Retrolental Fibroplasia, Arch. Ophth. **41**:553-561 (May) 1949.

baby is 6 weeks old, with no or low amounts of water-soluble vitamin A and ferric ammonium citrate. Their daily dose of alpha tocopherol acetate was 150 mg. given by mouth. Blood serum levels of vitamin E do not constantly correlate with the occurrence of retrolental fibroplasia. Their reasoning for the validity of the use of vitamin E, while well presented and logically stated, was based on a small series and consequently is statistically vulnerable.

The great variety of opinion here summarized is probably due to the lack of study of early stages of microscopic material and to the fact that early microscopic and clinical material have not been combined in the same study. Neither has a comparison been made of laboratory and clinical material from normal premature infants and of premature infants showing the disease. It is felt that an attempt should be made to classify the pathologic reaction of fibrosis behind the lens as a syndrome. An analysis of the material, based on the nature, location and progress of the early pathologic changes, will show whether unification as a syndrome is valid.

MATERIAL FOR THE STUDY

The material analyzed falls into three main groups: (1) ocular and other tissues removed at autopsy from infants of premature birth; (2) ocular tissue showing sporadic cases of retinopathy, postlenticular fibrosis of several types and subclasses, and (3) ocular tissue showing the retinopathy of premature birth, with general postmortem studies in some cases. Clinical studies were made in each of the three groups.

EYES OF UNAFFECTED PREMATURE INFANTS

Ophthalmoscopic studies of "normal" premature infants when compared with those on full term infants showed fundi consistent in appearance with the conceptional ages of the infants and the presence or absence of a hyaloid artery or other fetal vessel. The vessels were normal in size; no abnormality of transparency was seen in the retina. An exception was an occasional retinal hemorrhage, the frequency of which increased somewhat in infants born near term. Infants born after cesarean section, free from the molding factors, showed no retinal hemorrhages. Observations of this sort are difficult to make and require the employment of a fixation forceps to immobilize the globe and the use of external pressure near the limbus to permit visibility in the region of the ora serrata. Adequate dilation of the pupil is difficult to obtain.

Forty eyes of fetuses of four to nine months' gestation were studied microscopically. They showed differentiation consistent with their gestation ages. None showed retrolental fibrosis or significant changes in the retina. Corresponding to the age of development were the hyaloid

artery, postlental and anterolental vessels, the transparency of the secondary vitreous and retinal structures. The retina, according to its degree of prematurity, showed loose coaptation and the usual variable anterior insertion. An occasional well contained hemorrhage was seen in the retina. No excess of vascular tissue; no disrupting, heavily staining, marked edema, and no vitreal hemorrhage was noted.

SPORADIC RETROLENTAL FIBROSIS

From a series of 75 eyes examined microscopically was selected a representation of sporadic retrolental fibroplasia sufficient to permit a classification. These laboratory studies were combined, when possible, with clinical observations and observations on other patients from whom laboratory material was not obtained. Analysis of this material showed that the sporadic form of retrolental fibroplasia occurs as three main types: (1) in the region of the lens and hyaloid fossa, (2) primarily in the retina with secondary late retrolental fibrosis and (3) as a retrolental fibrosis incidental to various causes.

Sporadic retrolental fibroplasia of the lens–hyaloid fossa type is congenital and shows slightly progressive unilateral fibrosis, which starts in the lens or its fossa. This fibrosis varies in degree from an exaggerated hyaloid attachment to a fibrous tissue–filled fossa. Other parts of the eye are not necessarily involved. The manifestation is monocular in full term infants. The cause of this type of fibrosis can be related to delayed regression of the hyaloid membrane, complicated by a fibrous attachment of the lens and anomalous vascular tissue. This type is similar in character to congenital cataract and is amenable to the same treatment.

Any defect in the posterior capsule of the lens is liable to show a posterior epithelial plug and variable proliferations of vascular fibrous tissue. The posterior capsule of the lens may have been congenitally thin and later ruptured. A partial failure of development of the posterior capsule of the lens usually occurs at about the 13 mm. (5 to 6 week) stage. An abnormally thin posterior capsule is also vulnerable to rupture from adhesion and intrusion of the vascular hyaloid before or near the 40 mm. (9 week) stage. Rupture of the capsule may also be due to the growth of secondary lens fibers and traction of the zonular lamella at the 70 mm. (3 month) stage. In all these conditions the lens is usually well suspended, and the secondary lens fibers show variable cataractous changes.

The third type consists in primary fibrosis of the lens due to fetal injury of maternal origin. The involvement is usually bilateral. Other ocular tissues often show atypical development and degenerative changes, which continue after birth. Multiple congenital defects of the heart, brain and other structures accompany the ocular defects as a

rule, and these have been interpreted in the recent past as congenital dysplasias. Microscopic sections of these eyes show defects in ocular development and retrograde changes. The fetal cataract caused by maternal rubella during the first trimester of pregnancy is an example of this type of defect. Other maternal diseases may cause similar, but less selective, lesions.

The fibrous cataract may also be due to a maternal cause. It lies midway in degree between the cataract following maternal rubella and that due to severe fetal uveitis and microphthalmos. The disk of the fibrous cataract is usually connected by fibrous tissue to the ciliary processes, and commonly it is displaced somewhat to one side. It is thought that the initial damage was done to both the primary and the secondary lens vesicle by a toxin. Mesenchymal tissue sometimes survives in the hyaloid fossa behind the fibrous cataract. Rarely, a white central proliferative zone can be seen clinically, and lying outside this are masses of fibrous tissue made by the epithelium of the secondary lens vesicle. An additional variant is a congenital morgagnian cataract. In this condition primary lens fibers have developed properly but there has been liquefaction necrosis of the secondary lens fibers. Usually the anterior chamber is deep because the diseased lens is drawn posteriorly by fibrous bands. If the cataract has formed during the primary lens vesicle stage, it dates between the 12 and the 24 mm. (5 and 7 week) stage. If the process has begun during the developing secondary lens fiber stage, it dates at the 25 mm. (7 week) stage.

Very severe fetal ocular disease of maternal origin will cause degenerative changes of advanced microphthalmos. The degree of destruction may even go far enough to cause secondary anophthalmos.

PRIMARY SPORADIC RETINAL DISEASES

In primary retinal diseases a fibrosis behind the lens may appear as a late reparative or degenerative manifestation. Full term infants and juveniles show this monocularly. The causes are many—inflammations, vascular diseases, new growths and congenital lack of differentiation. Parasitic worms are an important cause of endophthalmitis in children (Wilder[12]). Some specimens show excessive or massive fibrosis in the late stages of repair. A report on massive separation of the retina in infants and juveniles will be published separately.

SECONDARY RETROLENTAL FIBROPLASIA INCIDENTAL TO MULTIPLE CAUSES

In this group retrolental fibrosis is an incident in the course of a pathologic repair. The causes are diverse and many. Eyes so affected are fully differentiated. Primary points of attack are usually the anterior

12. Wilder, H. C.: Endophthalmitis, Transactions of Pan-American Medical Association, 1950, to be published.

segment, the lens and the uveal tissue. Separation of the retina often precedes the formation of the postlental membrane.

RETINOPATHY OF PREMATURE BIRTH

Three stages of retinopathy of premature birth will be described briefly, both clinically and microscopically: (1) the primary retinal disease, (2) the stage of involvement of the vitreous and separation of the retina, (3) the stage of late pathologic repair and atrophy. The microscopic studies will be illustrated by photomicrographs.

Primary Retinal Disease.—Early clinical signs of retinal involvement have been observed two or three days after birth and as late as the fifth month. In the early stages one eye is sometimes more involved than its fellow. Since the clinical signs of the early stages are limited to those seen with the ophthalmoscope, the time of beginning is difficult to determine. The early pathologic changes seen clinically are patches of lessened retinal transparency, often seen near the ora, engorged retinal vessels and sometimes visible hemorrhage. The early changes progress and show exaggerated, dilated vessels and hemorrhages. Some fundi show vascular proliferations on the surface of and within the retina, accompanied with edema and loss of transparency. Externally the eyes show no congestion. A delicate haze or cloud may be seen in the vitreous. The disease was not seen to develop after the seventh month except in a monocular sporadic form. The size of the eye is normal for the age of the infant. Bilaterality is the rule, and the hyaloid artery and other fetal vessels may be present, independent of the conception age and the degree of prematurity at the time of the examination.

The earliest microscopic signs of the disease in the retina can be seen at birth. These signs are intense protein edema, hemorrhage, dilated blood channels and vasoformative tissue. These abnormalities cause extensive separation of the retinal elements. Hemorrhage is seen here and there usually, but is not always a conspicuous part of the process. Vasoformative tissue, remaining pretty much in its field of origin, like hamartoma,[13] is disproportionately present. The thin-walled blood channels do not show progressive growth but are aberrant and precocious, unduly large and proliferative and in the phases of early active congestion push aside retinal tissue. Occasional rupture through the internal limiting membrane is noted. Thinness and some incompleteness are characteristic of the internal limiting membrane of the retina in the sections. The choroid shows only intense choriocapillary congestion. In rare instances hemorrhage originates from a branch of the long ciliary artery within an edematous, swollen ciliary process.

13. By "hamartoma" is meant accumulations of vascular tissue, normal in location but excessive in amount and without the property of malignant growth.

An illustrative case of early primary retinal involvement is summarized as follows:

Case A.—*Clinical History.*—The infant was born between one and two months prematurely; the age at operation was eighteen hours. The weight at birth was 1,600 Gm. The patient was the mother's second child. There was a history of preseparation of the placenta and of cesarean section for abdominal pain.

Pathologic Report on Eye (figs. 1-10).—The eye showed immature development, as indicated by the structure of the cornea, the development of the angle and iris, the presence of a pupillary membrane, the globular structure of the lens, the presence of postlental hyaloid vessels, the development of the ciliary body, a well marked anterior redundant position of the retina and the presence of the hyaloid artery. The chief pathologic condition was concerned with congested and leaking vaso-

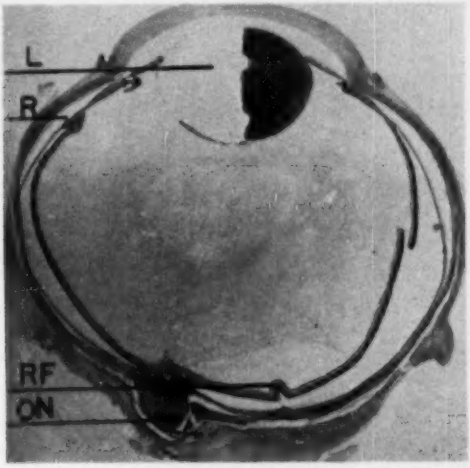

Fig. 1 (case A).—Early (reversible) stage of retinal vascular disease of prematurity. The infant was born by cesarean section after seven months' gestation; age at operation was 18 hours; weight at birth, 1,600 Gm. *L* indicates fetal lens; *R*, retina, separated by hemorrhage located well forward on mesial side and showing fold (*RF*) near nerve head; *ON*, optic nerve and persistent hyaloid artery. The retinal hemorrhage is well contained; no organized vitreous or retrolental membrane appears at this early stage.

formative tissue in the retina. There had been moderate breaking through of blood into the vitreous, but free hemorrhage lay under and separated the retina. Engorgement was noted throughout the uvea. It was particularly intense in the retina, the choriocapillary layer of the choroid and the ciliary processes, where some hemorrhage was noted. The diagnosis was retinopathy of prematurity, in the early, reversible stage.

Stage of Vitreous Organization and Retinal Separation.—The clinical signs in the middle stage of the retinal disease show partic-

ipation by the vitreous, as indicated by increasing cloudiness and the formation of fibrillae. The vitreous serves as a spreading matrix for fibrosis, which arises in the edematous retina and fans out in arcs and bands. The general direction taken by these minute fibrillae and strands is anterior and posterior, following somewhat the curve of the globe. The visible origin is often anterior, sometimes temporal or mesial.

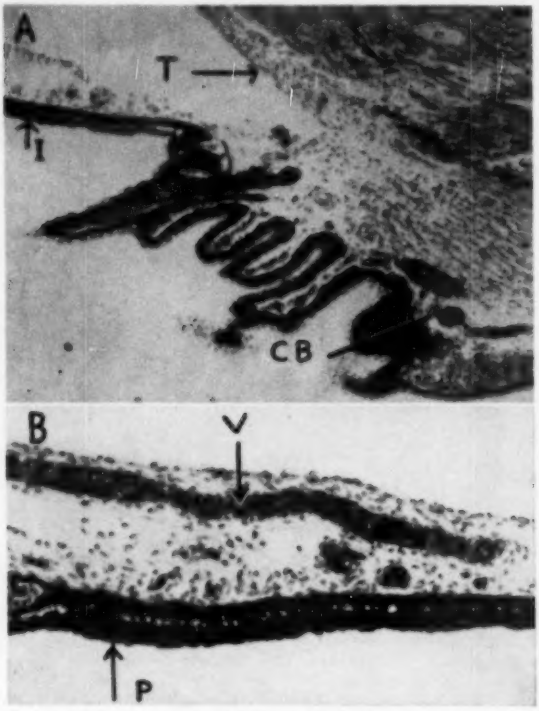

Fig. 2 (case A).—*A*, congested ciliary body with hemorrhage *(CB)*, fetal sclerocorneal trabeculum *(T)* and iris *(I)*, with partly coapted posterior pigment layers.

B, fetal iris. *V* indicates congested vessels, with no hemorrhage; *P*, posterior pigment layers, not fully coapted.

In a matter of days, countless minute, hairlike fibrillae, so numerous as to appear like a cloud or a haze, are seen connected with larger arcuate bands. When the mistlike fibrillae in the vitreous have developed to the point of organization and the retina is partially separated, the process cannot reverse. Coarser subsidiary and connective cross bands soon

form connections with the retina. The retina inevitably gives way and is pulled axially, and is drawn into a retrolental funnel, sheath or ball. This change is accomplished in a matter of four to sixteen weeks. In patients who show limited hemorrhage in the retina and less in the vitreous the process may be reversed. In still others the process stops after formation of a retinal fold, and the roughly round or oval random hemorrhages can be seen to resolve before the arcuate vitreous bands

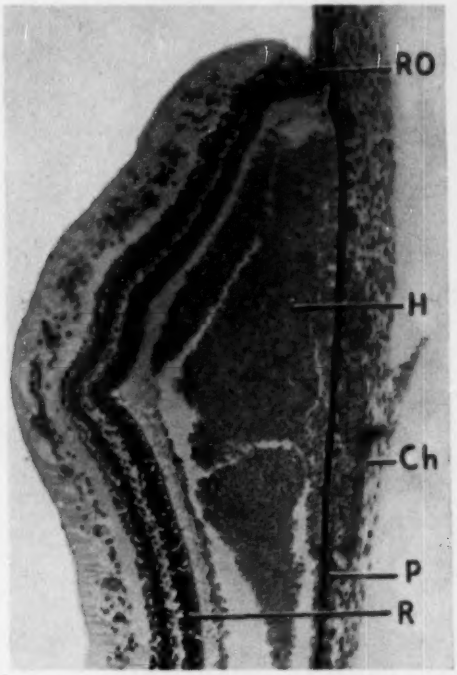

Fig. 3 (case A).—Anterior attachment of retina: *RO*, is ora serrata; *H*, intraretinal hemorrhage; *Ch*, choroid; *P*, intact pigment epithelium of retina on thin lamina vitrea; *R*, well differentiated retina, including inner and outer limiting membranes.

develop. The most favorable clinical prognosis has been noted in patients in whom the hemorrhage and exudation are held in the retina. In these eyes the internal limiting membrane apparently has not been broken through, and there is no vitreous to participate in visual destruction.

The microscopic tissue changes observed in the subacute, nonreversible stages are fibrovascular proliferations in the retina and vitreous;

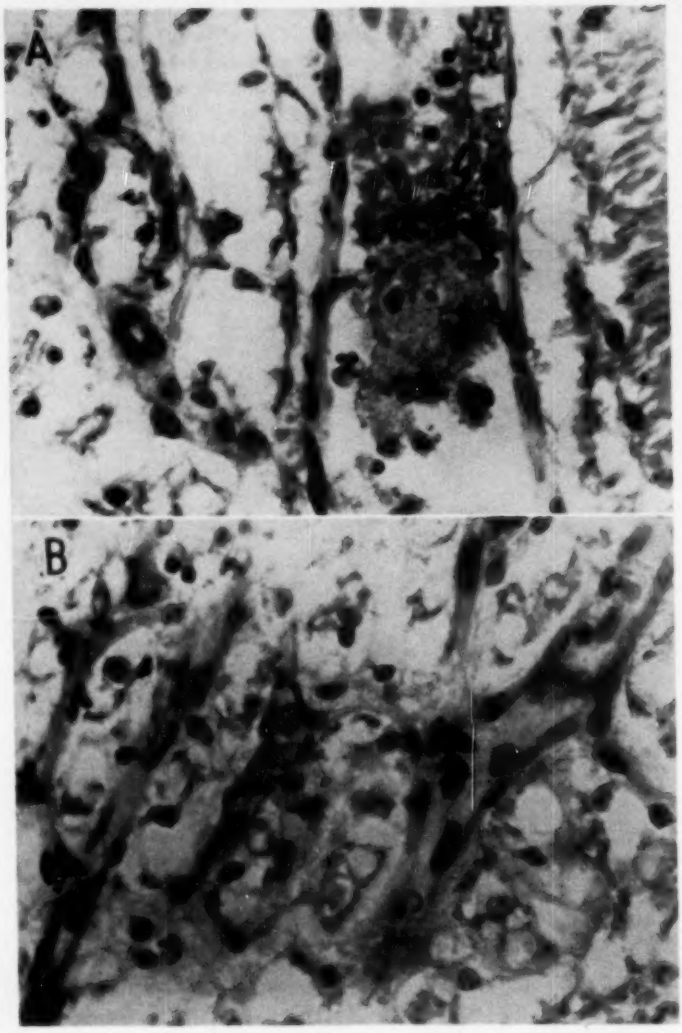

Fig. 4 (case A).—*A*, retina, cut partly on the flat, showing dilated vessels, neovascular tissue and nerve fiber and ganglion cell layers separated by edema. *B*, retina cut on the flat, with vasoformative tissue; × 650.

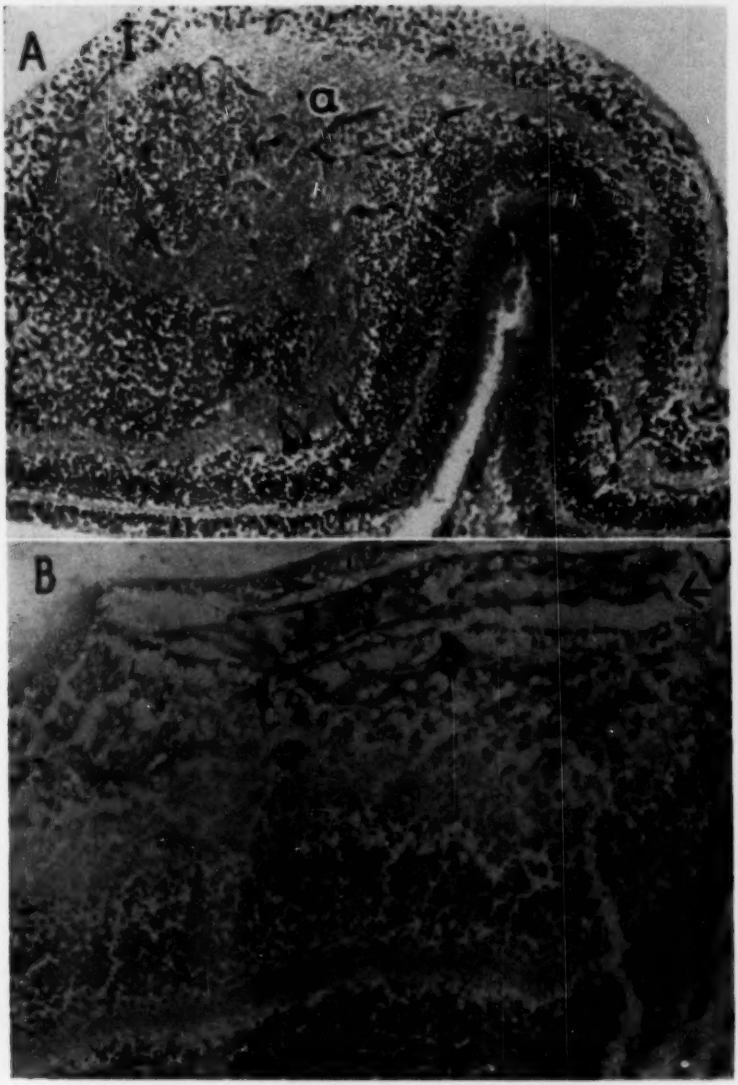

Fig. 5 (case A).—*A*, retinal fold. *I*, indicates incomplete inner limiting membrane, and *a*, vasoformative tissue in edematous nerve fiber layer. × 113.

B, retina. *V* is greatly dilated vessel parallel to and below the ruptured inner limiting membrane; below the long vessels are numerous dilated capillaries and edema, as deep as the outer nuclear layer.

Fig. 6 (case A).—Separation of nerve fiber and ganglion cell layers of retina by edema and vasoformative tissue (*VF*). *INL* is inner nuclear layer.

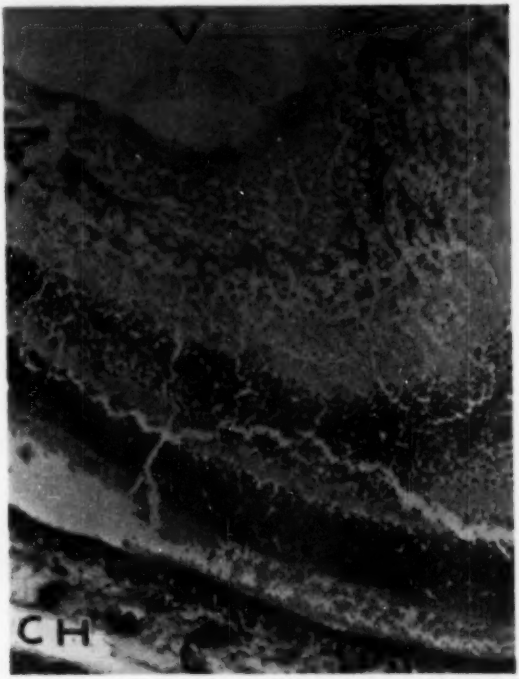

Fig. 7 (case A).—*V*, proliferative angiomatous tissue breaking through inner limiting membrane of retina; exudate and hemorrhage. *CH* indicates choroid.

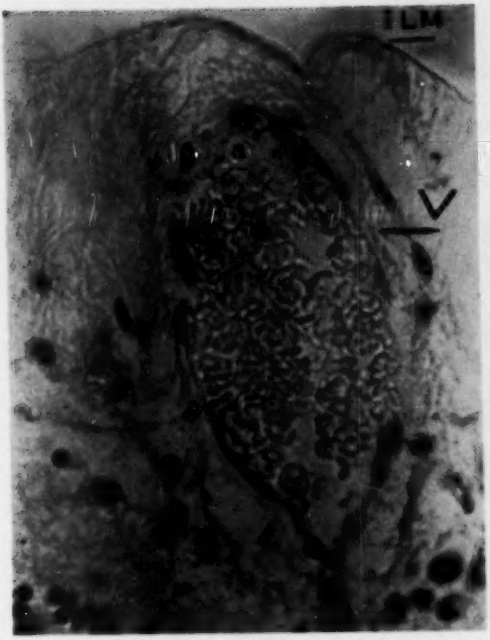

Fig. 8 (case A).—Engorged vessel displacing inner limiting membrane of retina. *V*, vessel; *ILM*, inner limiting membrane. × 650.

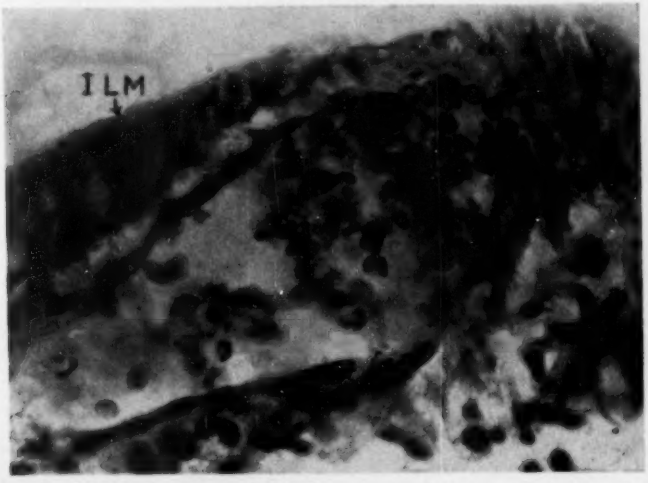

Fig. 9 (case A).—Engorged retinal vessel showing rupture and hemorrhage at point of breaking through an incomplete inner limiting membrane (*ILM*).

retinal folding and secondary occlusions of small arterioles are succeeded by more hemorrhage, limited necrosis and fibrosis. The retina is pulled into an axial position or is balled behind the lens. Sections from eyes

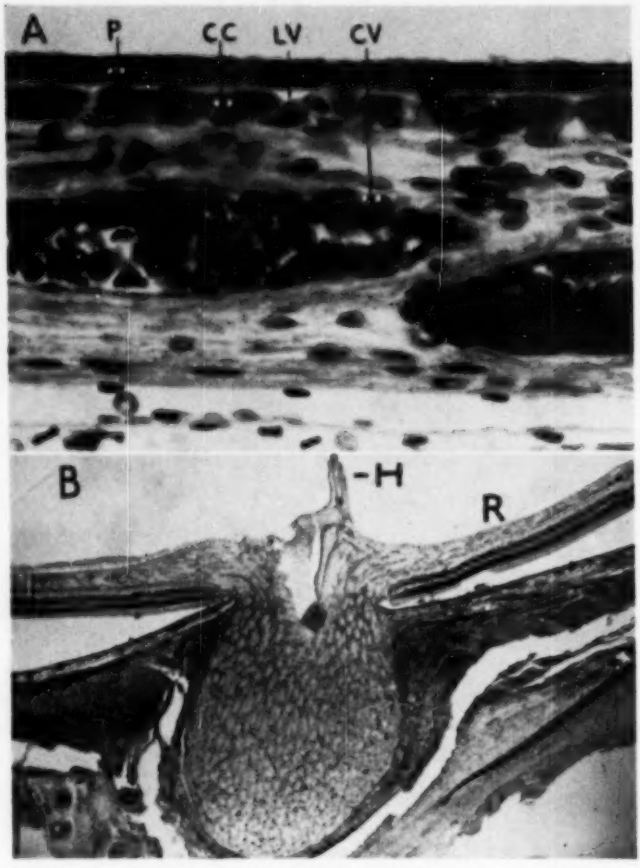

Fig. 10 (case A).—*A*, choroid. *P* is pigment layer of retina; *CC*, congested choriopapillary layer; *LV*, lamina vitrea; *CV*, large choroidal vessel.

B, nerve head showing hyaloid artery (*H*) and well differentiated retina (*R*). Separation of retina from choroid is an artefact. × 25.

in older stages show retinal blood vessels entering the inner layers of the retina by branching and seemingly budding, with considerable

increase of mural cells. In other sections endothelial tubes lie on the inner surface of the retina, and in still others, within the nerve fiber layer. The hamartomatous character of the neovascular tissue is apparent. A few fat-laden macrophages may be noted. In the fossa behind the lens both glial and mesenchymal fibrosis is more or less uniformly present. The fibrous sling has incorporated the ciliary processes and the lens. It is conceivable that when this diaphragm contracts the lens is pushed forward and the anterior chamber becomes shallow.

An illustrative case of a late stage of the retinopathy of prematurity is summarized.

Case B.—*Clinical History.*—The infant was born thirteen weeks prematurely; the weight at birth was 3 pounds 7 ounces (1,505 Gm.), and the age at operation

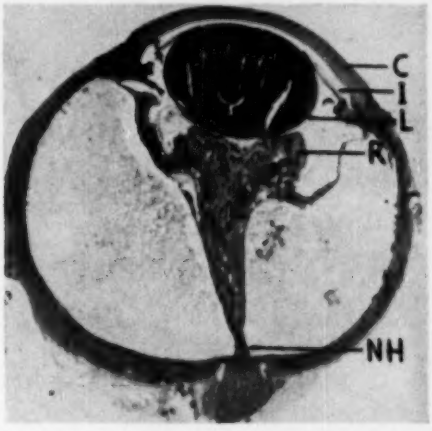

Fig. 11 (case B).—Eye of infant born thirteen weeks prematurely with older stage of retinal vascular disease of prematurity affecting both eyes. Age at operation, 9 months; weight at birth, 3 pounds 7 ounces. *C* is infant cornea; *I*, infant iris; *L*, lens; *R*, retina, axial and balled behind the lens; *NH*, nerve head, dragged inward.

was 9 months. There was no glaucoma. In the left eye, the better one, the pupil dilated well; many blood vessels were seen diverging from the central region, and the ciliary processes were heavily pigmented. The right eye showed a synechia; the ciliary processes were not visible. This eye was smaller than the left; the anterior chamber was shallow. Searching nystagmus and fetal blue iris were present in both eyes.

Pathologic Report on the Eye (figs. 11 to 13).—The anterior chamber was largely obliterated. The retina was completely separated and disorganized behind the band of retrolental fibrosis and participated in its formation. Behind the separated retina was noted acidophilic granular material. Vasoformative tissue entered the inner surface of the retina and had proliferated within the retina. The choroid showed colloid excrescences.

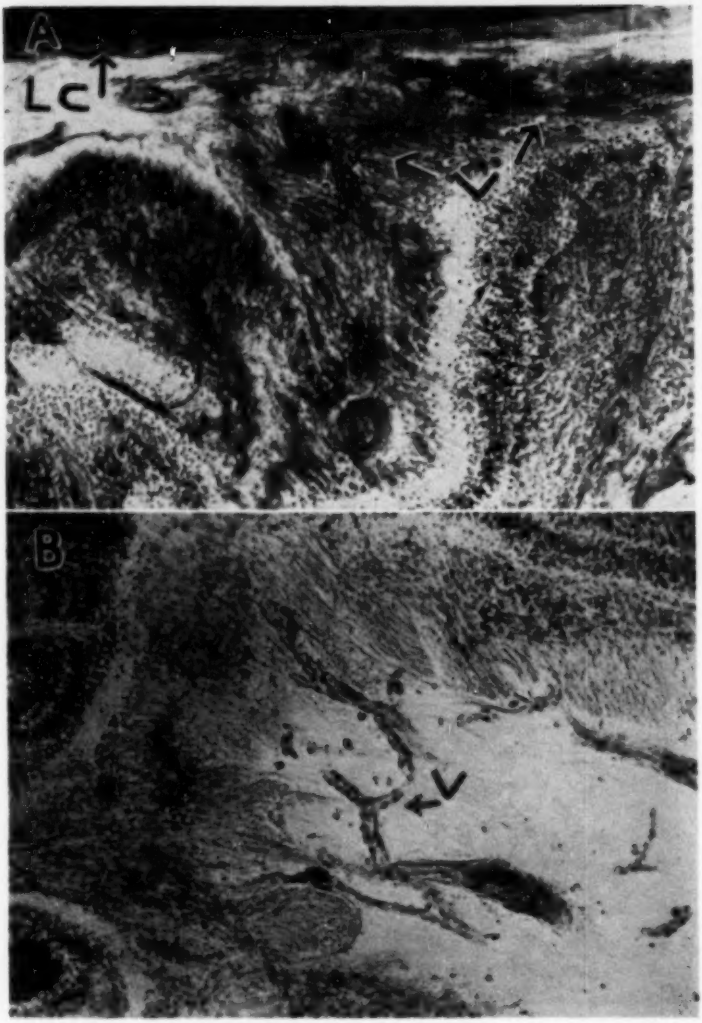

Fig. 12 (case B).—*A*, lens capsule (LC), with older vessels in retrolental balled retina.

B, neovascular formation (*V*) on inner surface of retrolental balled retina.

Necropsy.—The findings, in part, consisted of hamartomas involving the leptomeninges over the base of the brain and the upper cervical portion of the cord, the cornu ammonis, the floor of the third ventricle and the pons and growing within the third ventricle. The foramens of Monro, Luschka and Magendie and the third ventricle were obstructed by hamartoma; cerebral edema and extreme hydrocephalus, diffuse bilateral cerebral deficiency, emaciation and malnutrition were noted.

Late Stage of Degeneration and Atrophy.—In the late stages, as seen clinically, the organized vitreous has pulled the retina off, and more or less atrophy of the globe is present. Behind the lens the intravitreous fibrous proliferations connect with the ciliary processes to form a contracting diaphragm. Both fibrous tissue and ciliary processes are usually drawn inward and together show serrations when viewed anteriorly. The lens and iris are well forward; sometimes the lens touches the cornea. A searching nystagmus has often developed. Ultimately, the angle is blocked by the iris as the anterior chamber becomes shallow. Secondary glaucoma may be present. In some cases the iris has changed color as a result of degenerative processes. During this stage the infant commonly holds its knuckles firmly against the lids—possibly because the mechanical stimulus gives a sensation of light or because it gives relief from discomfort. The clinical appearance in these late stages is often similar to that of retinitis proliferans and atrophy after severe common inflammatory processes. The eyeball is atrophic and has become smaller. The globe appears to be set back in the orbit, resembling a state of enophthalmos. There is a definite impression of orbital atrophy.

In the late stages of the retinopathy of prematurity the blood vessels of the retina are microscopically contracted; the walls often show hyaline thickenings. Proliferations and migration of pigment are variably seen in the portion of the retina left with the choroid. There is an inescapable resemblance in some sections to the disorganized retina of retinitis exudativa (Coats's disease) and in others to the vascular reaction of angiomatosis retinae. As a rule, there is less lipid activity of cells in the process in infants than is seen commonly in the juvenile or the adult form of angiomatosis. Sometimes there can be seen patches or nests of cells, macrophages, many lipid laden, usually outside but sometimes within, the outer retinal layers. Cysts, varying from small to large, develop within retinal structures and contribute to its disorganization. Superficial vascular proliferations in the retina are seen in most patients. The changes seen in general are those which follow protein exudation, hemorrhage, organization, proliferation, glial fibrosis and atrophy. The blood vessels which persist near the lens show thickened walls. The retrolental tissue is more fibrous in the late stages and, combined with elongated ciliary processes and separated retinal remnants in a dense

sling, seems to force the lens into the shallowing anterior chamber and against the cornea. The angle is thus blocked, and the probability of secondary glaucoma has been realized. Some infants show relief from enucleation of the blind, painful eye. Rarely do such eyes show enlargement. Glaucoma is a secondary complication, occurring late and of mechanical origin. The over-all atrophy of the globe is shown by microphthalmos. Associated congenital defects which may be present are rare and incidental.

An illustrative case of a late stage of retinal and vitreal repair and atrophy is reported.

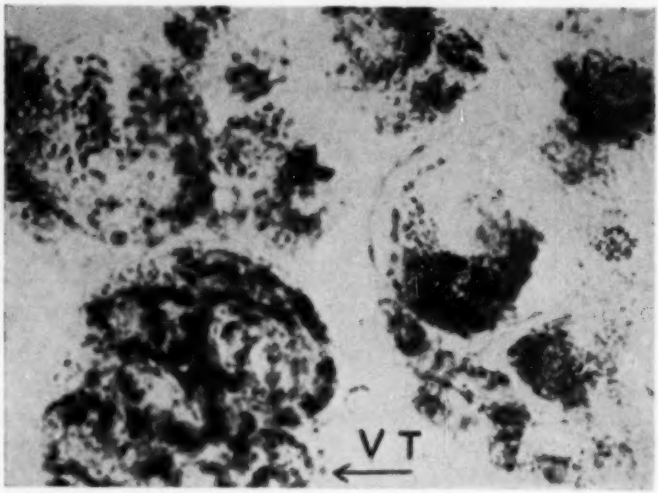

Fig. 13 (case B).—Vascular retinal disease of prematurity, older stage, with angioform proliferations in retina. × 650.

Case C.—The infant was born six weeks prematurely, the age at the time of operation being 4 years.

Pathologic Report on Eye (figs. 14 and 15).—Examination revealed old adhesions of the iris; well marked vascular retrolental membrane; blood vessels, somewhat hyaline in character; some recent hemorrhage; numerous cholesterol clefts adjacent to the membrane, and many new-formed vessels near the lens. The epithelial nuclei of the lens extended well posterior. Subcapsular cataractous changes were posterior. The retina had been dragged inward and had balled back of the lens, with disintegration and fibrosis. Marked fibrous proliferations were present in the organized structure of the vitreous, and recurrent episodes of hemorrhage were evidenced by laminations. Sheetlike calcification was well under way in the choroid. There was well marked proliferation of the pigment epithelium.

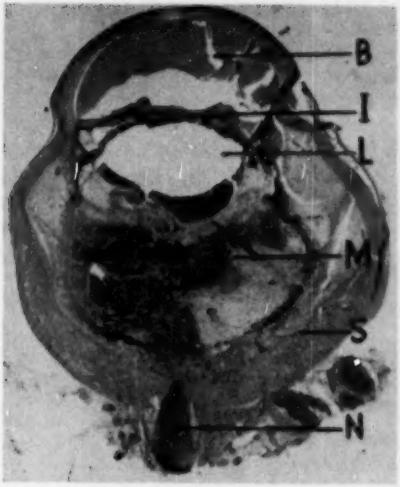

Fig. 14 (case C).—Eye of infant born six weeks prematurely, with late stage of retinal vascular disease of prematurity (phthisis bulbi). Age at operation, 4 years. The globe was pulled inward at the limbus, and the lens was drawn posteriorly by shrinking membranes, producing a deep anterior chamber (*B*); the anterior chamber contained old and new hemorrhages. *I*, is iris; *L*, lens; *M*, complicated membrane, complete destruction of the retina and late pathologic repair containing calcium and cholesterol; *S*, thickened sclera; *N*, atrophic optic nerve.

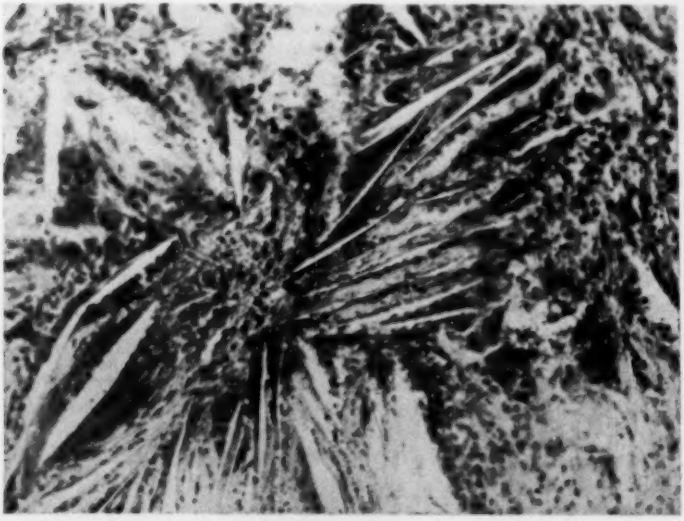

Fig. 15 (case C).—Detail of late stage in a case of recurrent hemorrhages, showing calcium deposits and cholesterol clefts. × 150.

In general, the eye illustrated a late, atrophic stage of recurring uveitis and the retinopathy of prematurity, with excessive organization, hemorrhage, cholesterol formation and calcification.

CLASSIFICATION

The early stages of ocular disease of infants are dissimilar; the late stages tend to resemble one another. Because of this, a classification has been constructed as much as possible from early lesions. An attempt has been made to classify retrolental fibroplasia as a syndrome on the basis of nine factors, namely, frequency, age of onset, progression, degree of ocular differentiation, bilaterality, the principal site of origin, primary cause, associated general defects or diseases and the effects of treatment. The material roughly falls into two main groups: (1) sporadic retrolental fibroplasia, with its subclasses and types and (2) retrolental fibroplasia as a reaction to the retinopathy of premature birth. The subtypes and classifications may be seen in the outline to follow:

I. Sporadic retrolental fibroplasia

- A. Primary in the lens and hyaloid fossa region
  1. Remnants of hyaloid vessel and fibrosis
  2. Defect in posterior lens capsule with fibrosis
  3. Injury to fetal lens of maternal origin (including fetal cataract, fibrous cataract and microphthalmos with fibrosis)
- B. Primary disease in the retina; secondary retrolental sclerosis
  1. Undifferentiated retina and secondary vitreous with retinal folds and separation, seen in full term infants
  2. Massive retinal separation due to edema, hemorrhage, cystoid changes and fibrosis, seen in full term infants
  3. Massive separation secondary to inflammation
  4. Retinal angiomatosis in both juveniles and young adults, and other new growths

II. Primary retinal disease related to premature birth

COMMENT: RETINOPATHY OF PREMATURITY

There were striking differences between the sections from the retinas of normal premature infants and those showing retinopathy. The eyes from normal premature infants showed rare, but well contained, intraretinal hemorrhages. Not seen were widely distributed angioid changes and intense congestion with hemorrhage and edema separating the retinal elements. In some postmortem specimens taken from normal premature infants the factors of compression and molding from maternal labor could be considered causative of some hemorrhage, in spite of the small size of the fetus. However, after postmortem experimental injection of latex into the carotid artery of a nonviable prematurely born infant, sections of the eyes showed the mass in the vessels of the choroid, to some extent in vessels of the ciliary body and optic nerve and only slightly in the retina—the substance in all instances being well contained.

	Sporadic Occurrence of Retrolental Fibrosis		C. Incidental Retrolental Fibroplasia Multiple Causes	Retrolental Fibroplasia of Premature Birth
	A. Lens-Hyaloid Fossa	B. Retinal Origin		
Frequency	1. Persistence of hyaloid vessel with fibrosis in fossa; rare 2. Defective posterior lens capsule; rare 3. Congenital cataract with fibrosis, maternal in origin (sometimes epidemic); rare	1. Retinal separation, undifferentiated type; rare 2. Massive separation of retina, edema type; rare 3. Massive separation of retina, hemorrhagic type; rare 4. Massive separation of retina, cystic type; very rare 5. Retinal separation from angiomatosis; rare	Occasional	Common; incidence varies with degree of prematurity and environmental factors —0 to 80%
Age of onset	1. Failure of posterior vascular capsule of lens to regress—3-4th and 9th month 2. 9th week or third month of fetal life 3. 1st to 3d month of fetal life	1. Undifferentiation, congenital 2. Full term, congenital in infants or during first year 3. Full term, infants and juveniles 4. Juveniles 5. Juveniles and young adults	Any age	Clinical onset 1st to 3d month, up to 7th month; has been observed 3d day after birth; microscopically has been found the first day of birth
Progression	1. Relatively fixed 2. Relatively fixed 3. Usually fixed, sometimes progressive to phthisis	1. Fixed 2. Progressive 3. Progressive 4. Slowly progressive 5. Progressive	Progressive	Usually progressive; early stages can reverse
Degree of ocular differentiation	1. Vascular remnants and hyperplasia; retina normal usually 2. Usually complete, except lens 3. Retina intact; microphthalmos—multiple defects common	1. Undifferentiated, other defects common 2. Differentiated 3. Differentiated 4. Differentiated 5. Differentiated	Complete	Varies with degree of prematurity and age when examined; retina usually differentiated
Bilaterality	1. Unilateral usually 2. Unilateral 3. Bilateral (may be unilateral)	1. Unilateral 2. Unilateral 3. Unilateral 4. Bilateral 5. Unilateral	Unilateral	Bilateral
Principal site in the eye	1. Lens and fossa 2. Lens and fossa 3. Lens and fossa	1. Primary retina and vitreous 2. Primary retina 3. Primary retina 4. Primary retina 5. Primary retina	Anterior segment and retina	Retina Secondarily in vitreous
Primary cause	1. Nonregression of fetal vessels 2. Weak or undifferentiated posterior capsule 3. Maternal disease (sometimes virus)	1. Any causes relating to lack of differentiation 2. Increase in vascular permeability to serum 3. Increase in vascular permeability to blood 4. Constitutional disease—involvement of bone 5. Familial vascular disease (angiomatosis)	Any cause of exaggerated pathologic repair	Susceptibility due to prematurity; increased permeability of neovascular tissue; noncontained hemorrhage, organized vitreous and retinal separation
Associated general defects or disease	1. None 2. None 3. Often cerebral; cardiac and other anomalies	1. Variable, usually none 2. Ocular only 3. Ocular only 4. Extensive bone disease; dwarfism 5. Cerebral involvement, frequently cerebellum	None unless incidental	Metabolic deficiencies; hamartoma
Treatment (ocular)	1. Window operation through lens and membrane 2. Window operation through lens and membrane 3. Cataract surgery if lens is differentiated	1. None known 2. None known 3. None known 4. None known 5. Diathermy of retina (genetic prevention)	None or enucleation	Prevention; search for maternal and fetal metabolic causes; for the older forms —none

Three possible origins of the retinal disease seen in infants of premature birth are, first, maternal disease; second, the susceptibility of the premature infant to structural and metabolic faults, and, lastly, postnatal care before the eighth gestation month. Obscure possibilities of maternal causes of the fetal disease exist. Maternal bleeding did not correlate in the large series reported by Kinsey and Zacharias.[8] In their series, placenta previa was found to be the principal cause of maternal bleeding, whereas the frequency of maternal bleeding with and that without retinopathy were about the same statistically. A follow-up of our series of microscopic material on retinal disease related to prematurity has not shown a necessary relation to maternal illness or bleeding during gestation. If a maternal factor were present, it would alter fetal tissue on the basis of the time of action in utero. This was true in the group of primary fibroplasia in the lens-hyaloid fossa region and is illustrated by fetal cataract caused by maternal rubella. The two potentials of reversibility and progressiveness found in the retinal disease of prematurity weigh heavily against maternal factors. If prematurity alone were the adverse factor, then one would note a uniform, country-wide distribution. The disease does not increase with prematurity in some parts of the world. In other areas the incidence of survival of prematurely born infants has not increased, whereas the retinal disease has. Three significant facts to consider are low birth weight, age at time of appearance of the disease and reversibility. With these three factors and prematurity itself in mind, it is likely that structural incompleteness and the unstable, precocious demands of metabolism in prematurity are coupled with certain induced factors. The anterior loop of uncoapted, redundant retina lying over the ciliary body, sometimes over the ciliary processes, is in a region of the greatest ocular growth and activity. This segment of the eye is rapidly growing forward, away from the retinal insertion. The ciliary body and processes are simultaneously differentiating; the lens is flattening as the zonular suspensory apparatus begins to function. All these activities may be said to lie in an undifferentiated fetal matrix.

One may well ask: What precipitates the proliferative reactions? Do these present a particular morphologic picture and course? Why are reversals in the process sometimes noted? Why do some types of retrolental fibroplasia appear, even though rarely, in older children? To find the answers to some of these questions, it is necessary to use analogy and to compare the pathologic processes of the premature retina with the responses seen in other tissue. The premature infant begins life in oxygen earlier than the normal infant. His metabolic abilities are precarious and exaggerated. His weight is often low, and structural and growth mechanisms are abnormal or faulty, on the basis of underdevelop-

ment and excessive demands. The chemical processes of embryonic retinal cells presumably are different from those of the mature cells. A different chemical structure of embryonic retinal tissue is indicated by its deeply basic-staining properties. The retina is overly anterior, not completely differentiated and loosely coapted. The vitreous is coarsely fibrillar. These metabolic and morphologic factors can be related to the case at hand.

In analogous controllable experiments, as seen in tissue cultures, the behavior of cells and their growth can definitely be related to the environment. In the cultures, proliferation begins in the presence of known growth-promoting chemical substances, coupled with the removal of certain morphologic obstacles to growth. Nutritional elements, catalysts, oxygen supply and chemical growth-promoting substances are stimulating factors. Obstacles to growth are a high concentration of cells in a state of tissue equilibrium, that is, a compact structure, often contained within definite limiting membranes—a closed system. Growth is induced in cultures by tissue dissociation, by reducing the cell concentration. After such a displacement, the cells, by proliferation and growth, gradually again convert such an open system into an equilibrium by forming a compact, dense structure. In other words, the cells concentrate again by growth. Likewise, the mature retina is a more or less closed-in tissue, owing to the concentration of its cells, nerve fiber layer, supporting Mueller's fibers and, especially, containing and limiting membranes. However, the immature retina is especially susceptible to structural displacement. It is not fully differentiated, and its membrane boundaries are faulty or incomplete. The retina, thus, is a source of proliferating material, which serves to seed the vitreous and become a continuum with it. There are four principal causes of retinal cell dissociation consistent with proliferative ability and viability of this membrane, namely, edema, hemorrhage, neoformed vascular tissue and undifferentiation of supportive structure. The hamartomatous vascular tissue is not limited to the eye. In addition to these stimuli for growth and proliferation from displacement, the young secondary vitreous forms a favorable fibrous tissue culture medium (fig. 16). The stimulus for growth caused by the separation of cells and the favorable fibrillary and vasoformative matrix are important physical arrangements for proliferation. Without the proliferation of the vitreous and its aftermath of separated retina, the retinal disease of premature birth would be a focal process showing areas of local repair and scarring.

The retinas of affected premature infants, both in the living eyes and in sections, show edema. The edema is albuminous in the early stages, and later, judging from staining reactions, larger molecules of globulin and fibrinogen enter the extravascular tissue because of increased capillary permeability. The causes of altered capillary permeability may be many, including raised venous pressure, lowered plasma protein con-

centration, oxygen deficiency, disturbance in water and electrolyte disposal and altered lipid and calcium metabolism—a process generalized as retinosis.

Retinal hemorrhage, commonly seen clinically and noted in sections, quite possibly is due to increased capillary permeability arising from structural changes. These changes are, hypothetically, altered intercellular cement substances and damage to endothelial cells and the basement membrane. Conceivably, lack of oxygen transportation from an imbalance of chemical substances ascribed to this role is fundamentally at fault.

Fig. 16.—Fetal vitreous matrix, somewhat condensed, stained for elastic tissue; × 1,200.

Reversibility of the process is clinically seen to be proportional to the degree of involvement of the vitreous. Vitreous hemorrhage alone, while not good, is not necessarily indicative of complete destruction. Well established proliferative response in the vitreous causes retinal separation and inevitable precarious visual function. The potential for reversibility probably indicates that the process is not due to an embryonic defect. Reversibility could represent a low degree of primary involvement, or a process at the level of cell metabolism. In this case a process of disintegration of retina and of the vitreous can be stopped by the removal of a metabolic insufficiency. The attainment of sufficient structural support for the vascular tissue of the retina would aid in preventing serous and hemorrhagic leakage.

Early objective signs in the clear media of the living infant's eye can be seen, and studies of the media consistently show the lesions described in the retina and vitreous. The loss of transparency in the retina and vitreous, the visible hemorrhage and vascular and fibrous proliferations, sometimes outlined by blood stain, and the elevation and separation of the retina can be seen and followed stage by stage. The earliest pathologic change, however, is seen only microscopically.

The sharp drop in incidence after the seventh month of gestation is explained by the relative tissue and metabolic maturity achieved by this time. The tempo of high metabolic activity in a rapidly growing embryonal structure has been altered and slowed to the relative stability of a mature differentiated retina.

Treatment for the retinal disease of prematurity lies mostly in the field of prevention. Evaluation of any treatment must meet the test of a significant lowering of the incidence of the disease. A lower incidence, to be significant, must outstrip the wide normal variations in manifestation of the disease. The decrease in manifestation without treatment in a given area has ranged from 15 to 60 per cent. Probably some of the factors concerned are prevention of low birth weight, prematurity itself and factors in the environmental care of the premature infant. A matrix for development of the disease is concomitant with prematurity and is present at birth. By matrix I mean excessive, nonregressive retinal vascular tissue susceptible to pathologic permeability. Metabolic management is a possible source of preventive treatment. Whether or not the vascular leakage gets out of the retina and leads to organization of the vitreous depends partly on the maturity of the retina. Further studies of the premature infant may show what combinations of oxygenation and nutrition will promote early structural maturity and reduce permeability. Adrenocorticotropic hormone (ACTH) has shown some early promise, but at the time of writing its use is experimental.

The ocular treatment of the child with a late, hopeless stage of the disease is governed by his comfort and appearance. Enucleation is advisable when obvious discomfort and pain arise in the eyes. His social and educational managements demand understanding and a long range program. Most of the children can be trained and educated toward a life of happiness and usefulness. Some have limited mental equipment and crippling organic disease.

CONCLUSIONS

Retrolental fibroplasia is a rare proliferative fibrous reaction primary in the lens and its fossa; it is also a secondary angiofibrous manifestation of retinal disease. These processes are sporadically found in full term infants, children and juveniles. In addition, a similar fibrosis can be an incidental reparative reaction to ocular injury at any age. Retrolental fibroplasia also commonly occurs in prematurely born infants of low

birth weight as a secondary manifestation of primary retinal disease. The primary disease is an edematous, hemorrhagic and proliferative process associated with hamartomatous neovascular tissue in the retina, a process best described as the retinopathy of premature birth.

Therefore the term retrolental fibroplasia as commonly used is descriptive of nonspecific pathologic reactions. The term inadequately describes a phase of the late stages of some diseases and but part of the primary process of others. Consequently, retrolental fibroplasia is not a syndrome or a disease entity. The term is best used to describe one phase of pathologic reaction.

The earliest clinical signs of the retinopathy of prematurity, as seen with the ophthalmoscope, are engorged vessels, edema and occasional hemorrhage in the retina. In later stages elevations of the retina are accompanied with loss of transparency. These signs can occur from a few days to weeks or months after birth. The primary retinal lesion may become stationary. It can reverse, in inverse proportion to involvement of the vitreous. The process may be arrested when a retinal fold has been made or at the level of a small retinal scar without clinical sign. The secondary manifestations seen in the vitreous are a haze, a dotlike opacity, fibrillae, strands and bands. The second stage clinically begins with involvement of the vitreous. The vitreous organizes and pulls the retina off axially and forward until it lies behind the lens, where a fibrovascular membrane develops. At this late stage a dentate fibrosis can be seen behind the lens, often connected with the ciliary processes.

In the late clinical stages the anterior chamber becomes shallow because the lens is pushed forward by the contracting fibrous diaphragm. Glaucoma may develop. In some patients the lens even touches the cornea. The late stage is one of more or less atrophy of the globe and the appearance of enophthalmos.

Microscopically, early stages of the retinopathy of prematurity show hamartomatous vascular tissue, extensive dissociation by protein-rich edema and hemorrhage. The retinal structures are separated and loose, especially at the ora serrata. The internal limiting membrane is incomplete. Postmortem studies show hamartomatous changes elsewhere in the body. These pathologic and anatomic changes can be seen at birth. In the secondary stages of the disease retinal destruction is completed by a fibrous organization of the vitreous from edema, hemorrhage and angiomatosis.[15] The loose retinal tissue organizes with a fibrillary vitreous; this organization follows the same principles as those governing tissue cultures. Subsequent contraction leads to separation of the retina. The retrolental membrane is derived from the organized vitreous and the gliosed retina. The process may become stationary, or may reverse

15. By angiomatosis in this connection I mean capillary and fibroglial proliferations, not malignant growth.

before the stage of organization of the vitreous. That this may be accomplished, the increased vascular permeability must stop and the support of mature tissue be achieved.

The late microscopic stage of the retinopathy is one of atrophy. The blood vessels are small; some areas show angioform proliferations; mineral deposits are usually present, and the globe is small.

The uneven distribution of the retinopathy of prematurity over the country is explainable on the basis that the disease is fundamentally a susceptibility coupled with prematurity, and that regional differences in incidence are due to local environmental and metabolic factors. It is possible that the retinal disease of prematurity becomes clinically manifest only because of a complicated nutritional imbalance induced in the environment. To minimize metabolic derangement, early feeding to prevent loss of weight and to promote maturity of tissue is indicated. The early and prolonged use of oxygen seems logical. Whatever will prevent excessive permeability of neovascular tissue is indicated.

No maternal causes are known at the time of writing. Whether preventive treatment should be predominantly on the maternal or on the infant side remains to be discovered. When the retinal disease of prematurity has progressed to the second stage and shows considerable retinal separation, only symptomatic treatment is indicated. However, much may be done in the educational and social fields for such affected children.

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ABSTRACT OF DISCUSSION

Dr. Algernon B. Reese, New York: The term pseudoglioma, or pseudoretinoblastoma, has been applied to a heterogeneous group of lesions in infants and young children characterized by a white pupillary reflex due to the presence of opaque tissue in the vitreous cavity. Dr. Heath uses the term retrolental fibroplasia to refer to this group as a whole. I think he is right in wishing to supplant the term pseudoretinoblastoma, but I doubt the wisdom of using "retrolental fibroplasia" to cover this group because this term has become firmly fixed to designate the lesion which has increased tremendously in the past decade or more in premature infants. I prefer the term leukocoria, meaning "white pupil," to indicate this condition.

Dr. Frederick Blodi and I analyzed a series of cases similar to that which Dr. Heath has studied and we are in close accord.

The condition which is of paramount interest now is Dr. Heath's "retinal vascular metabolic disease of prematurity," or our "retrolental fibroplasia." This is a disease which has increased so much in incidence that it is now the commonest cause of blindness in preschool children. Dr. Heath believes, as we do, that the lesion is congenital, although it most assuredly progresses after birth. It is important to determine whether the lesion is congenital or acquired, because this issue determines whether investigative efforts regarding the cause are directed

toward the mother or the infant. We believe that the disease is congenital, for the following reasons:

1. The microphthalmos is of a greater degree than it would be had the growth of the eye been interrupted at the third to the fifth month of life.

2. In many of the cases a true pupillary membrane arises from the collaret of the iris.

3. The disease is associated with hemangiomas of the skin in 20 per cent or more of cases, and these hemangiomas are present at birth.

4. When fraternal twins are affected, usually only one has the disease. Were the lesion acquired, the result of some method of treatment of the infants or an environmental factor, then both twins would be expected to have the disease.

5. We have not had a single instance in which a sibling had the disease. In many instances, certainly, premature siblings received the same postnatal treatment as did the child affected.

6. The available pathologic material indicates that a vascular tissue in the vitreous produces hemorrhage with organization.

7. In both Terry's series and ours, the disease has been noted at birth.

8. Dr. Heath found the vascular matrix in the eye of a premature infant removed eighteen hours after birth. We have examined microscopically the eyes of 14 premature infants weighing less than 4 pounds (1,814 Gm.) at birth and have found the vascular matrix in 1 case.

The criticism could be leveled at Dr. Heath's classification that his is based almost entirely on histologic specimens, most of which are necessarily in an advanced stage of the disease for which the eye was removed. The end stages of these processes are all somewhat similar in that the retina is detached and pulled forward into scar tissue back of the lens. In our classification, we have tried to consider the clinical, as well as the pathologic, aspects of the disease, and to use the pathologic specimens in so far as they might throw light on the fundamental pathologic process.

DR. PARKER HEATH, Boston: Where there seems to be differences of opinion as to origin and progress of the disease among observers, these may largely be resolved by the study of early lesions, both clinically and microscopically. Similar conclusions are inescapable by those who follow the retinopathy of prematurity from its very earliest stages, seeing the infants day by day and thus noting the progress in different groups. One group of infants will not show the lesion in its ultimate stage, and the other will. Patients who do show the ultimate lesion with a membrane back of the lens have had retinal hemorrhage as a dominant feature associated with excessive vascular tissue, and the pathologic response to hemorrhage in the vitreous as proliferation has been inevitable. We were fortunate to be able to study a wealth of early clinical and pathologic material.

I agree with Dr. Reese that the name "retrolental fibroplasia" is probably here to stay. However, I felt constrained, in making my classification, to use obvious, conventional terminology, descriptive of the pathology, as I would with any other tissue.

RESULTS OF OPERATION FOR CATARACT WITH PRIMARY GLAUCOMA

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THE MANAGEMENT of patients with senile cataract and primary glaucoma is a major ophthalmologic problem. At present there is much diversity of opinion concerning the treatment. Some of the more important questions to be resolved by the ophthalmologist confronted with this problem may be noted.

1. Would a simple cataract extraction control the intraocular tension in the case of an untreated eye in which primary glaucoma and cataract are present?

2. If the intraocular pressure cannot be controlled by miotics or operation for glaucoma, should another fistulizing operation be performed at the same time that the cataract is extracted?

3. Is the intracapsular or the extracapsular technic the method of choice in cases of senile cataract with primary glaucoma?

The present study was undertaken to determine whether the experiences with cases of senile cataract and primary glaucoma in the State University of Iowa clinic could contribute to the solution of this recurrent and frequently vexatious problem, one which has not received sufficient attention.

MATERIAL AND METHODS

One hundred cases in which cataract extractions were performed in eyes with primary glaucoma were gathered for this analysis. In some of these cases some type of fistulizing operation had been done prior to the cataract extraction, the time interval between the two operations varying from two months to twelve years. In another group of these 100 cases only miotics were used prior to the cataract extraction. In a third group no treatment for the elevated intraocular pressure was received before the cataract operation. All these cases satisfied the criterion that each patient be followed for at least six months after the cataract extraction, or for the same minimal time after the last surgical procedure if an operation had been performed for glaucoma after cataract extraction.

In all but 2 of the 100 cases the glaucoma was in the noncongestive phase before a cataract operation was performed. Cataractous changes in these cases

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ranged from the incipient through the intumescent, mature and hypermature stages. Cases of secondary glaucoma as the result of an intumescent or morgagnian cataract, as well as cases of all other types of secondary glaucoma, were not included in this analysis.

Except for minor modifications, the technic employed in cataract extraction was uniform throughout the 100 cases. Preoperative preparation of the patient consisted in induction of akinesia after the O'Brien technic, retrobulbar injection of procaine hydrochloride, 2 per cent solution, with epinephrine hydrochloride 1 : 20,000 and topical instillation of 5 per cent cocaine hydrochloride. A speculum was used in every case, and a canthotomy and superior rectus suture were employed whenever needed. Incision was usually made with a keratome and enlarged with scissors. However, the Graefe knife or sclerotome was used whenever the occasion demanded. In all cases some form of iris surgery was performed, the procedure usually not involving the sphincter. Delivery of the lens through a round pupil was practiced whenever feasible. Forceps, and in a few cases suction with the Dimitry apparatus, were employed in delivery of the cataract. In every case an intracapsular cataract extraction was attempted. This was achieved in 75 cases (75 per cent). The incision was closed by some type of corneoscleral suture except in those cases in which a filtering operation had been performed at the time of the cataract extraction. In such cases suturing of the conjunctival flap sufficed.

The operations were performed by members both of the resident and of the senior staff.

Tension was measured by the Schiøtz X tonometer. An intraocular pressure of 22 mm. of mercury or less was considered as satisfactorily under control.[1] No cataract extraction was performed in an eye with acute congestive glaucoma. However, of the 100 cases there were 2 in which the glaucoma was in the chronic congestive phase and cataract extraction was performed. In the remaining 98 cases the glaucoma was of the chronic noncongestive type.

ANALYSIS OF RESULTS

Of the 100 cases, glaucoma was controlled in 92 after cataract extraction. In 68 of these 92 cases the intraocular pressure remained under control without further medication. In 16 cases the use of miotics

1. We realize that operative success in reducing intraocular pressure is by no means always synonymous with success in preserving visual function.

In most of the cases presented in this paper determinations of visual acuity and fields were included in our postoperative examinations. With few exceptions, no further loss in visual function took place after the intraocular pressure was reduced to and maintained at 22 mm. of mercury or less. In a very few cases visual acuity and fields did continue to deteriorate despite "normal" tensions. The presumption was that normal tension was too high for such eyes, and we usually attempted further to reduce the intraocular pressure by medication or surgical procedures.

In treatment of glaucoma all methods are directed toward the lowering of intraocular pressure, through which one expects preservation of the eye from further deterioration in visual acuity and fields. There is no known procedure which is directed toward the specific improvement of visual acuity or fields alone. So long as one is, through insufficient knowledge, constrained to treat primary glaucoma symptomatically, and not etiologically, one is forced to evaluate results primarily by the amount of reduction in tension, and only indirectly by the effect on vision and visual fields.

was required, and in 8 the pressure was controlled only after one or more cyclodialyses had been performed. In the remaining 8 of the 100 cases the intraocular pressure could not be controlled after cataract operation and the condition proceeded to absolute glaucoma.

The 100 cases are divided into the following groups:

GROUP 1.—Chronic congestive glaucoma not controlled with miotics (2 cases).

Both patients were admitted to the ophthalmic service with a tension of approximately 60 mm. of mercury. Instillations of miotics, including 2 per cent physostigmine salicylate; retrobulbar injections of procaine hydrochloride, 2 per cent with epinephrine hydrochloride 1:20,000; intravenous injections of 50 per cent sorbitol, and use of sedatives brought the tension down to 38 mm. of mercury in 1 case and to only 50 mm. of mercury in the other. An intracapsular cataract extraction combined with a peripheral iridectomy and anterior sclerectomy was performed in each case. In both cases the tension remained under control without further use of miotic therapy after the cataract extraction.

It has not been the practice in this clinic to perform a cataract extraction in an eye with chronic congestive glaucoma. The usual procedure adopted is to bring the glaucoma under control either with miotic therapy alone or by surgical intervention if necessary. After a period of approximately two months, when the globe has become quiet, a cataract extraction is performed. However, in these 2 cases the cataracts were mature, reducing the visual acuity to light perception only, while the fellow eyes were completely blind. It was thought advisable, therefore, to combine a cataract extraction with a fistulizing procedure. In both cases the postoperative reaction was more pronounced and the convalescence was prolonged. However, the resulting visual acuity and intraocular pressure were satisfactory. The favorable results in these 2 cases encourage us to try this procedure in other cases of chronic congestive glaucoma in which surgery is required and the cataractous changes have advanced sufficiently to warrant extraction.

GROUP 2.—Chronic noncongestive glaucoma not treated before cataract extraction (15 cases; table 1).

In 1 case the intraocular pressure before cataract extraction was 35 mm. of mercury; in a second, 45 mm. of mercury, and in a third, 50 mm. of mercury. In the remaining cases the intraocular pressure was 30 mm. of mercury or less. A fistulizing operation was performed at the same time that the cataract extraction was carried out in 5 of these cases, including the 3 cases in which the intraocular pressure was above 30 mm. of mercury. No attempt was made to control the intraocular pressure prior to the cataract operation. In all these cases, with 1 exception, the pressure was controlled without miotic therapy after the cataract extraction. In the case in which the tension was uncontrolled

the anterior chamber was lost on the day following a simple combined intracapsular cataract extraction. The anterior chamber remained unreformed during the entire ten postoperative days in the hospital. The patient failed to return at the prescribed time after discharge, and when

TABLE 1.—*Results in Cases of Chronic Noncongestive Glaucoma Not Treated Before Cataract Extraction*

Operative Procedure	Cases	Results After Cataract Surgery		
		Tension Controlled Without Miotics	Tension Controlled With Use of Miotics	Tension Not Controlled
Intracapsular cataract extraction with iridodialysis	4	4	0	0
Intracapsular cataract extraction with complete iridectomy	5	4	0	1
Extracapsular cataract extraction with complete iridectomy	1	1	0	0
Intracapsular cataract extraction with anterior sclerectomy	2	2	0	0
Extracapsular cataract extraction with anterior sclerectomy	1	1	0	0
Intracapsular cataract extraction with iridencleisis	1	1	0	0
Total no. of cases	15	14	0	1

TABLE 2.—*Results in Cases of Chronic Noncongestive Glaucoma in Which Tension Was Controlled with Miotics Before Cataract Extraction*

Operative Procedure	Cases	Results After Cataract Surgery		
		Tension Controlled Without Miotics	Tension Controlled With Use of Miotics	Tension Not Controlled
Intracapsular cataract extraction with iridodialysis	4	2	2	0
Intracapsular cataract extraction with peripheral iridectomy	2	1	1	0
Intracapsular cataract extraction with peripheral iridotomy	3	3	0	0
Extracapsular cataract extraction with iridodialysis	4	4	0	0
Intracapsular cataract extraction with anterior sclerectomy	1	1	0	0
Extracapsular cataract extraction with complete iridectomy	1	1	0	0
Total no. of cases	15	12	3	0

he was again seen, in four months, absolute glaucoma had developed. The globe was finally enucleated a year later.

GROUP 3.—Chronic noncongestive glaucoma in which the intraocular pressure was controlled with miotic therapy before the cataract operation (15 cases; table 2).

The duration of treatment with miotics in these cases varied from several days to several years. The intraocular pressure prior to the use of miotics varied from 25 to 58 mm. of mercury. After the extraction

of the cataract the intraocular pressure remained under control without further miotic therapy in 12 cases, whereas in 3 cases the additional instillation of 2 per cent pilocarpine nitrate was required for control. The type of iris surgery done at the time of cataract extraction apparently made little difference in the control of the intraocular pressure. A peripheral iridotomy was just as effective as an iridodialysis or a peripheral or complete iridectomy. In 1 case an anterior sclerectomy was performed with the combined cataract extraction. In retrospect, this procedure was deemed unnecessary in that case.

TABLE 3.—*Results in Cases of Chronic Noncongestive Glaucoma in Which Tension Was Controlled by Surgical Treatment for Glaucoma Before Cataract Operation*

Operative Procedure	Cases	Results After Cataract Surgery: Tension Controlled Without Miotics	Tension Controlled with Miotics	Tension Controlled by Operation	Tension Not Controlled
I. For glaucoma					
1. Cyclodialysis, single operation	22	13	3	1	1
2. Cyclodialysis, following other fistulizing operations	10	6	3	0	1
3. Cyclodialysis with iris inclusion in supraciliary cleft	2	2	0	0	0
4. Cyclodialysis with basal iridectomy	1	0	1	0	0
5. Lagrange anterior sclerectomy with peripheral iridectomy	2	1	1	0	0
6. Iridencleisis	5	1	1	1	2
7. Basal iridectomy	2	2	0	0	0
Total no. of cases	44	30	8	2	4
II. For cataract					
1. Intracapsular cataract extraction	32	24	6	1	1
2. Extracapsular cataract extraction	12	6	2	1	3
Total no. of cases	44	30	8	2	4

GROUP 4.—Chronic noncongestive glaucoma in which the intraocular pressure was controlled by glaucoma surgery prior to cataract extraction (44 cases; table 3).

The time interval between the operation for glaucoma and the cataract extraction varied from two months to fifteen years, the average being 3.3 years. Only in 10 of the 44 was the cataract extraction performed within six months after the operation for glaucoma. It has been the practice at this clinic to perform either a cataract extraction alone or the extraction with a fistulizing procedure (anterior sclerectomy or an iridencleisis) in cases of cataract and glaucoma if at the time of examination the lenticular changes are sufficiently advanced to warrant a cataract extraction. If the cataractous changes are early and the patient's visual acuity is satisfactory, miotics are given or, if necessary, one or more operations for glaucoma are performed for the control of the elevated intraocular pressure. If a cataract develops and the visual acuity

is reduced to the point at which operation is required after a decompressing procedure, a cataract extraction is performed, preferably not before an interval of two or more months has passed after the last operation for glaucoma. We believe this period of waiting is an important step in minimizing postoperative reaction. (The development of a cataract or a more rapid progression of cataractous changes following a decompression is commoner than one is led to believe from the literature.)

In 35 of the 44 cases in this group cyclodialysis or a modification of this procedure was done before extraction of the cataract. The incision for the cataract extraction was made at the upper portion of the limbus with a keratome in the usual manner and enlarged with scissors. However, for those cases in which a Lagrange iridosclerectomy, iridencleisis or a trephine operation had been performed and the drainage pathway was functioning, a corneal incision with a Graefe knife anterior to the filtering bleb, or an incision with a keratome and scissors lateral to it, was employed. Intracapsular extraction of the cataract was successful in 32 of the 44 cases. In 24 of these cases no further treatment was required. In the remaining 12 of the 44 cases the cataracts were extracted extracapsularly. In only 6 of these cases was no further treatment required for the control of glaucoma. It thus appears desirable to extract a cataract within its capsule in cases in which a fistulizing operation for the control of the intraocular pressure has been performed prior to a cataract extraction. An extracapsular extraction in any stage except the mature or hypermature phase would have a greater tendency to plug the surgically created drainage pathway through retention of capsule and cortical remains, thus increasing the postoperative reaction.

In 4 cases the glaucoma could not be controlled after cataract extraction. Intraocular pressure in 2 of these cases had been controlled prior to cataract extraction, in 1 by a single cyclodialysis and in the other by an unsuccessful iridencleisis followed by a successful cyclodialysis. Cataract extraction (intracapsular in 1 case and extracapsular in the other) was followed by postoperative iridocyclitis in each case. The reaction was controlled by cycloplegics and intravenous administration of typhoid H antigen. However, the intraocular pressure remained elevated. Another cyclodialysis was performed in each case several months after the globe was free of reaction, but without success. One eye underwent degenerative changes, and the process in the other eye went on to absolute glaucoma. Tension in the remaining 2 cases was brought under control with iridencleisis prior to cataract extraction. In each case the cataract was removed extracapsularly and the convalescence was longer than usual. In both cases the intraocular pressure became elevated after cataract extraction. An unsuccessful cyclodialysis was performed in 1 case, and absolute glaucoma eventually

developed. In the other case the eye remained irritable, the cornea became hazy and no further treatment was attempted. In 3 of these 4 cases an extracapsular extraction was performed, and in each much cortical material remained in the anterior chamber. The stage of cataract was incipient in 2 cases and intumescent in 1 case.

GROUP 5.—Chronic noncongestive glaucoma with the intraocular pressure uncontrolled by miotics or glaucoma surgery prior to cataract extraction (24 cases; table 4).

The intraocular pressure in all 24 cases after treatment for glaucoma did not exceed 32 mm. of mercury, the average being 27 mm. of mercury. The intraocular pressure prior to treatment with miotics or glaucoma surgery varied from 30 to 70 mm. of mercury, with an average of 48 mm. of mercury.

TABLE 4.—*Results in Cases of Chronic Noncongestive Glaucoma in Which Tension Was Not Controlled by Miotics or Operation for Glaucoma Before Cataract Extraction*

	Cases	Results After Cataract Surgery: Tension Controlled Without Miotics	Tension Controlled with Miotics	Tension Controlled with Surgery	Tension Not Controlled
I. Treatment before cataract extraction					
1. Miotics alone	6	3	1	2	0
2. Cyclodialysis and miotics	8	3	1	2	2
3. Cyclodialysis with basal iridectomy	1	0	1	0	0
4. Cyclodialysis with iris inclusion into supraciliary cleft	1	1	0	0	0
5. Iridencleisis	2	2	0	0	0
6. Trephine	2	0	1	1	0
7. Basal iridectomy	4	1	1	1	1
Total no. of cases	24	10	5	6	3
II. Type of cataract operation					
1. Combined cataract extraction	14	4	4	4	2
2. Cataract extraction with fistulizing operation	10	6	1	2	1
Total no. of cases	24	10	5	6	3

In 14 of the 24 cases a combined cataract extraction was performed. In 4 cases no further treatment was required for control of the intraocular pressure.

In the remaining 10 of the 24 cases a fistulizing operation was performed at the time of cataract extraction. In 6 of these cases no further treatment of the glaucoma was required.

It would appear from these results that in cases in which miotics or glaucoma surgery fails to control the intraocular pressure prior to cataract extraction some type of fistulizing operation performed at the time of the cataract extraction would be advisable.

There were 3 cases in this series in which the tension could not be controlled after cataract extraction. In 2 of these cases a cyclodialysis

failed to bring the tension down within normal limits. In the first case a combined intracapsular cataract extraction was performed. The anterior chamber was lost on the fourth postoperative day and remained shallow at the time of discharge, on the tenth postoperative day. The patient failed to return at the prescribed time, and when he was seen again, six months later, the eye was blind and the tension elevated. In the second case an anterior sclerectomy was performed at the time of the intracapsular cataract extraction. Later an epithelial downgrowth developed, despite radiation therapy, with loss of this eye. In the third case a complete iridectomy had been performed several months prior to treatment at the Iowa State University clinic. The tension was uncontrolled and remained elevated despite use of miotics. An intracapsular cataract extraction was performed, followed by severe uveitis. Absolute glaucoma eventually developed.

COMMENT

Several authors have reported satisfactory control of primary glaucoma after cataract extraction alone. Van Lint,[2] citing Elschnig, suggested that if the tension in an eye with cataract and glaucoma did not rise above 35 mm. of mercury, and if it could be reduced to 20 mm. of mercury with miotics, cataract extraction should be the first operation. Guyton [3] found, in an analysis of 44 cases of cataract and primary glaucoma, that if the glaucoma is noncongestive and can be controlled with miotics, or if it is of chronic congestive type, a combined cataract extraction should be the initial procedure, and is likely to be the only one necessary. Knapp,[4] in a series of 500 cases of cataract extraction, found primary glaucoma present in 9 before operation. The tension in 6 of these 9 cases was relieved by the cataract extraction alone, while in the remaining 3 cases miotics or operation for glaucoma was required to bring the tension under control. Ramsay [5] agreed with Elschnig and van Lint that in cases of cataract and glaucoma with a tension below 35 mm. of mercury which can be controlled by miotics, cataract extraction alone frequently results in "cure" of the glaucoma.

The results of our analysis are in agreement with the recommendations of Elschnig and van Lint that cataract extraction may be the initial, and often the only, operation necessary in cases in which the

2. van Lint, A., in Bailliart, P., and others: Traite d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 7, p. 677.

3. Guyton, J. S.: Choice of Operation for Primary Glaucoma Combined with Cataract, Arch. Ophth. **33**:265 (April) 1945.

4. Knapp, A.: Present State of the Intracapsular Cataract Operation, Arch. Ophth. **38**:1 (July) 1947.

5. Ramsay, G. A. S.: Glaucoma and Cataract, Arch. Ophth. **43**:195 (Jan.) 1950.

intraocular pressure is 35 mm. of mercury or less and is controlled by miotics. However, we would go further in saying that even in an eye in which the intraocular pressure initially is above 35 mm. of mercury but can be controlled by miotics a combined cataract extraction will control the intraocular pressure without further use of miotics or surgical treatment of glaucoma in a large percentage of cases. If, however, miotics alone will not control the intraocular pressure, a fistulizing operation, preferably cyclodialysis, should be performed first. The cataract extraction may then be performed two or more months after the operation for glaucoma. An alternative may be to perform an anterior sclerectomy or an iridencleisis at the time of the cataract extraction.

In cases in which neither miotics nor the initial operation for glaucoma controls the intraocular pressure, and the opacities in the lens have not advanced to the degree at which cataract extraction is necessary, further surgical treatment for glaucoma may be performed. Should the visual acuity of the patient be reduced to the point at which cataract operation is indicated, a cataract extraction combined with an anterior sclerectomy or iridencleisis has given satisfactory results—better results than when a combined cataract extraction alone has been performed.

There is some difference of opinion concerning the advisability of performing a filtering operation at the time the cataract is extracted. O'Brien[6] and MacMillan[7] have been pleased with this method. Wright[8] also recommended the method in cases in which glaucoma is uncontrolled. Kirby,[9] however, warned against this procedure, claiming that a filtering operation performed at the time of cataract extraction may delay the reformation of the anterior chamber, a complication which may lead to the formation of embarrassing anterior synechias.

There also exists a difference of opinion regarding the choice of the intracapsular and the extracapsular extraction technic in the removal of a cataract in the glaucomatous eye. Wright[8] and Holland[10] claimed that a cataract associated with glaucoma is not suitable for intracapsular delivery. Wright recommended that one should wait until

6. O'Brien, C. S.: Random Observation on Ocular Surgery, Quart. Bull., Northwestern Univ. M. School **18**:199, 1944.

7. MacMillan, J. A., in discussion on Ramsay, G. A.: Glaucoma and Cataract, Arch. Ophth. **43**:195 (Jan.) 1950.

8. Wright, R. E.: Lectures on Cataract: IV. Posterior Segment Complications in the Postoperative Period; Some Difficult Extractions, Am. J. Ophth. **20**:376, 1937.

9. Kirby, D. B.: Surgery of Glaucoma, Postgraduate Lectures on Ophthalmology, State University of Iowa Hospitals, June 14-19, 1948.

10. Holland, H. T.: Some Contraindications to the Intracapsular Operation for Cataract Based on 8,000 Cases of Intracapsular Operations, Indian M. Gaz. **57**:296, 1922.

a cataract matures before performing an extracapsular cataract extraction, the glaucoma meanwhile being controlled by miotics or surgical means if necessary. Knapp,[9] Pillat [11] and others, however, contended that intracapsular cataract extraction can be performed in cases with glaucoma with no additional hazards.

Modern technics and safety measures have made the intracapsular technic as safe as the extracapsular method, without the disadvantages of the latter. Our analysis shows that in cases in which previous operation for glaucoma has been performed the tension remains controlled after cataract extraction in a larger percentage of cases with the intracapsular technic than with the extracapsular method, and with fewer complications.

SUMMARY

Operative procedures in 100 cases of cataract and glaucoma are analyzed. The results and recommendations are summarized as follows:

1. In cases of chronic noncongestive glaucoma with the intraocular pressure controlled by miotics, regardless of its original height, a combined cataract extraction should be the initial operation, and is likely to be the only procedure necessary. The type of iris surgery apparently is unimportant.

2. If the tension is not higher than 35 mm. of mercury and a cataract operation is indicated, the extraction may be done without first attempting to control the tension.

3. If the tension is not controlled by miotics but a cataract extraction is indicated, a filtering operation combined with cataract extraction is recommended.

When the tension was not controlled by surgical treatment of glaucoma, a filtering operation combined with the cataract extraction gave better results in this series of cases than a combined cataract extraction alone.

In 2 cases of chronic congestive glaucoma with cataract, a cataract extraction combined with an anterior sclerectomy gave good results.

4. It is desirable to use the intracapsular technic in all cases of cataract extraction with primary glaucoma.

11. Pillat, A.: Intracapsular Extraction of Cataracta Complicata Accreta After Iridocyclitis and Glaucoma, Arch. Ophth. **42**:567 (Nov.) 1949.

MIGRAINOID HEADACHES

Their Ocular Manifestations

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HEADACHE is unquestionably the commonest and one of the most distressing ailments within the entire realm of medicine and, paradoxically, is even at the present time one of the least well understood; it has usually been considered an annoying accompaniment of many and diverse derangements of the human body, and its descriptions and analyses have been largely clinical and little concerned with its causative processes. Examination of many thousands of inductees into military service at the Boston Induction Station in World War II revealed that headache was the most frequent bodily complaint, and it was demonstrated that in over 50 per cent of persons who showed unfitness for service the chief complaint was headache. The implications [1] of this symptom may be serious or benign; and, although the intensity of the headache may bear little relation to actual tissue injury, failure to distinguish between the severe headache of subdural hemorrhage, cerebral abscess, brain tumor, meningitis or fever (which really constitutes a very small percentage of the total number of headaches) and the vast majority of head pains which spring from reversible body changes and psychologic and emotional episodes may have needless consequences and even endanger life itself.

In common with other specialists in the field of medicine,[1] the ophthalmologist receives more than his share of patients complaining of head pain. A few years ago, after seeing many patients with the typical so-called migraine syndrome, I became interested in this condition and in why this widespread symptom complex should in so many instances involve the eye. I began investigating the characteristics of this entity from a purely clinical standpoint and more than ever became impressed with its high incidence and striking ophthalmic side effects. The results of this study have recently been published.[1a] It was while

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Presented at a meeting of the New England Ophthalmological Society, Boston, March 15, 1950.

1. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

1a. Donahue, H. C.: Migraine and Its Ocular Manifestations, Arch. Ophth. **43**:96 (Jan.) 1950.

engaged in this work that I came on several interesting entities which simulate migraine to some extent and to which I should like to call attention.

MIGRAINOID HEADACHES

The past few years have brought forward four rather clearcut syndromes having characteristics resembling the migraine syndrome, some of which had previously been included in the category of migraine.

Histamine Headache.—Histamine headache was first described by Horton [2] in 1938. It is generally a unilateral headache, usually beginning in the later decades of life, is of short duration, commonly lasting less than one hour, and comes on frequently at night, one or two hours after the patient retires. It has no hereditary background. It is associated with profuse tearing and congestion of the eye on the same side, accompanied with rhinorrhea or stuffiness of the nostrils, increased surface temperature and oftentimes swelling of the temporal vessels of the involved side of the head. There is no associated nausea, vomiting or visual disturbance. Pain is the outstanding complaint; it is constant, excruciating and boring and involves the eye, the temple, the neck and often the face. Many afflicted patients contemplate suicide. It has a tendency to conform to the ramifications of the external carotid artery and differs from trigeminal neuralgia in not being related to the distribution of any cranial nerve. Pressure on the external carotid artery on the same side often gives relief; this procedure for relieving headache is an old, well recognized maneuver and is recorded in the early literature.

The pain is sometimes precipitated by the ingestion of alcohol, but not necessarily; some patients have become abstainers without obtaining a cure. It seems logical, however, that alcohol, being a vasodilator, would produce such a headache. Many patients have attacks only at night and are awakened from a sound sleep, night after night and week after week, at a certain hour. As the reclining position is intolerable some persons accustom themselves to sleeping propped up or in chairs.

Horton induced the typical head pain in 35 of 72 patients by injecting 0.1 to 1.2 mg. of histamine subcutaneously; the patients were unable to distinguish between the induced and the spontaneous attack, and it was never possible to induce such attacks by giving histamine to normal persons. Desensitization by repeated small doses of histamine diphosphate is the treatment he advocated for this condition; but no specific allergic or hypersensitive state has been demonstrated.

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2. Horton, B. T.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine: Preliminary Report, Proc. Staff Meet., Mayo Clinic **14**:257 (April 26) 1939; Collected Papers of the Mayo Clinic and the Mayo Foundation, edited by Richard Hewitt, Philadelphia, W. B. Saunders Company, 1940, vol. 32, p. 1048.

I believe, however, that histamine headache is very similar to true migraine headache and that its characteristic features are not clearly distinguishable from it; it most certainly conforms in pattern to a type of painful disorder of the cranial vessels; its occurrence, characteristics and course have considerable resemblance to those of migraine, and it could well be a form of true migraine.

Headache Associated with Muscle Ischemia.—The second entity was reported by Williams [3] in 1945. He described a type of pain referred to various parts of the head from localized painful areas in the muscles of the head and neck. The condition was first described by Froriep [4] in 1843 and was called myalgia. Lange [5] stated that macroscopic and microscopic examination of tissue excised from such tender areas of muscle showed no pathologic change, whereas other investigators expressed the belief that the pain from these muscles was caused by a chemical or a physiochemical stimulus, possibly histamine, and was referred over a definite region of the head. It resembles to a degree the head pain present in migraine, with which it is frequently confused. Williams studied 118 cases of this type at the Mayo Clinic and proposed the following criteria for diagnosis: (1) occurrence after the third decade of life, with onset often following acute infections, and (2) precipitation of symptoms by exposure to physical stimuli, such as drafts, changes in temperature or changes in atmospheric pressure. The pain is deep, not throbbing or sharp, and accompanied with localized areas of tenderness in certain muscles attached to the cranial bones. Associated with this myalgia are a neuralgia, usually involving branches of the fifth cranial nerve on the same side, and in certain cases evidence of vasodilatation, tinnitus and vertigo. It is possible that muscle ischemia is a factor in this pain, probably being induced by spasm of muscles of the neck and head. This type of headache was first treated by heat and massage; in fact, the condition probably gave rise to the so-called Swedish masseur. Williams,[3] in conformity with the possibility that this headache was due to a physical allergy associated with histamine, gave intramuscular injections of nicotinic acid for two to three months, and followed this with oral administration of the drug; complete relief was obtained in 54 of 72 cases. This type of therapy would point to muscle ischemia with vasoconstriction as a factor in the syndrome.

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3. Williams, H. L.: Syndrome of Physical or Intrinsic Allergy of Head: Myalgia of Head (Sinus Headache), Proc. Staff Meet., Mayo Clin. **20**:177, 1945.

4. Froriep, S., cited by Finch, J. E.: Report on Myalgia, Tr. Minnesota M. Soc., 1877, pp. 31-50.

5. Lange, M.: Die Muskelharten (Myogelosen): Ihre Entstehung und Heilung, in Lehmanns medizinische Lehrbücher, Munich, J. F. Lehmann, 1931, vol. 12, p. 194.

Headache Associated with Hypoglycemia.—The third condition was reported in 1949 by Wilkinson,[6] of the Mayo Clinic; he described a group of patients who had typical hemicrania and in some instances a rather characteristic aura, closely resembling migraine, which on careful investigation seemed to occur at a period during the day when the blood sugar was at a very low level. He called this condition hypoglycemic headache, or headache due to hyperinsulinism.

In 1935 Gray and Burtness[7] described headache of a migrainous character which was associated with hypoglycemia. While their criteria for hypoglycemia (60 to 90 mg. per hundred cubic centimeters) may be questioned by some, there appeared to be a definite connection between the blood sugar level and the beginning of the attack. Frequent feedings of certain foods prevented the attacks, while they could be precipitated by hypoglycemia induced with insulin. Of the 38 patients reported, 22 were described as having "true migraine."

Slight attention was given to this report, although Girard and Collesson[8] reported another series of cases of unilateral headache associated with hypoglycemia. Porges[9] and Földes[10] reported low carbohydrate and high protein diets as being of benefit in migraine, but apparently they did not associate this with the accepted method of treating spontaneous hypoglycemia.

Wilkinson[6] reported the following case:

> A man aged 30, a graduate student, stated that he had had "migraine headaches" for fifteen years. These were preceded by an "aura." The headache was located oftenest in the right or the left temporal area, was accompanied with scotomas, nausea and vomiting and lasted from several hours to as long as three days; they came on two to four times a month. The patient was treated by three different physicians for "migraine headache." He had never had any relief from ergotamine tartrate.
>
> The family history was without significance except that the father, paternal grandmother and two brothers had had "migraine headaches."
>
> Physical examination revealed an entirely normal condition. When seen in the clinic, the patient was loath to discuss his headaches and stated that if they could not be stopped he planned to leave school. Close questioning gave the following additional information: The so-called aura consisted of a feeling of weakness, drowsiness and fatigue; this was followed by nervousness, tremor and wet palms; sometimes he saw lights during the period. About one hour after the onset of

6. Wilkinson, C. F.: Recurrent Migrainoid Headaches Associated with Spontaneous Hypoglycaemia, Am. J. M. Sc. **218**:209, 1949.

7. Gray, P. A., and Burtness, H. I.: Hypoglycemic Headache, Endocrinology **19**:549, 1935.

8. Girard, J., and Collesson, L.: Migraine et perturbations glycémiques, Presse méd. **47**:705, 1939.

9. Porges, O.: Die Behandlung der Migräne mit kohlehydratbeschränkter Kost, Med. Klin. **33**:664, 1937.

10. Földs, E.: Migränebehandlung mit kohlehydratarmer Diät., Klin. Wchnschr. **18**:390, 1939.

drowsiness his headache would start and increase to a severe unilateral throbbing ache, usually in the right or the left temple. The patient had noticed that food taking prior to the onset of the nervousness might abort the headache.

Because of this suggestive history, the patient was given a glucose tolerance test. The findings showed that between three and four hours after the beginning of the fasting period the blood sugar level fell to 17 mg. per hundred cubic centimeters; a headache came on at this time and lasted about twelve hours. On several other occasions the patient had glucose tolerance tests; but, whereas the lowest level was at the three or four hour period, it never fell below 40 mg. per hundred cubic centimeters; each time, however, a headache was precipitated.

The patient was placed on a diet of 150 Gm. of protein, 190 Gm. of fat and 75 Gm. of carbohydrate. His headaches ceased except for two attacks, and both followed breaks in the diet. The patient, when seen fourteen months later, stated that he had had no other recurrence and had been free of the attacks twenty-four months after the diet was instituted.

Because of the dramatic result following treatment of the spontaneous hypoglycemia in this case, glucose tolerance tests were made in cases of headache in which there was the slightest possibility that spontaneous hypoglycemia existed.

Eleven of a total of 92 patients seen in a period of seventeen months had headache of a migrainous character that seemed to be associated with spontaneous hyperinsulinism; 2 received almost complete relief on the high protein, low carbohydrate diet, but headache continued to occur at infrequent intervals; these attacks appeared to be characteristic of the histamine headache described by Horton and responded to desensitization with histamine. It was necessary to continue the diet, however, as the headaches returned when the diet was discontinued; with the combined treatments complete recovery was obtained. A third patient obtained relief for two months, at which time nausea developed in association with pregnancy and the patient could not take the diet for almost a month. The headache occurred three times during this period; with cessation of the nausea and resumption of the diet the headaches were again controlled. Two patients had hypoglycemic symptoms at about the time the low blood sugar level was reached; neither had headache or received benefit from the diet. This emphasizes that the headache must be reproduced in the test before the diagnosis can be made.

Only 3 patients gave a history commonly associated with hypoglycemia, namely, weakness, sweating, dizziness and nervousness; in every case the patient stated that an "aura" preceded the headache, but careful questioning revealed that the aura was not a true one. Hypoglycemia was suspected in the other patients because the headaches usually started in midmorning or midafternoon; in 1 patient they occurred only on Sunday morning, and it was discovered that he varied his usual breakfast of bacon and eggs to waffles and syrup on Sunday morning.

Because of the relatively high incidence of this condition in a series of 92 patients suspected of having migraine headache, it is felt that the syndrome should be stressed and that with care a number of patients supposedly suffering from migraine may be more correctly classified and treated.

Vascular Headache.—In 1949 another important syndrome was reported by Alpers and Schlezinger.[11] These authors described several cases of unilateral recurrent headache, persisting in some instances only a few days and in others for months or years, and regarded as migraine. They studied 7 cases in particular in which oculomotor paralyses developed in conjunction with the headaches. The type of head pain which the authors described was not different from that encountered in any type of the so-called vascular headache, but the distinguishing feature was the presence of isolated extraocular muscle paralyses, which in most cases involved the third or fourth cranial nerves and which in the reported cases indicated an aneurysm of the posterior communicating artery, demonstrated by arteriography. As such aneurysms are usually small, the authors stated the belief that they constitute a favorable type for ligation, and they reported successful operative procedures in 5 of the 7 cases. They concluded that the diagnosis established from the clinical history of headache and the demonstration of ophthalmoplegia involving the third nerve, and sometimes the fourth, represents another of the types of hemicrania which, through more careful study and investigation, has been removed from the category of migraine.

Recently, in February 1950, Jaeger,[12] of Philadelphia, reported an analysis of 31 cases of aneurysm of the intracranial carotid artery which presented symptoms of migraine-like headache and involvement of the third cranial nerve and stated the opinion that these combined symptoms were sufficient to permit a presumptive diagnosis of such an aneurysm. Other observers have recognized and discussed this combination of symptoms, and several have commented on the relation of the etiology and symptoms of aneurysm of the intracranial carotid artery to those of ophthalmoplegic migraine. No one has defined the factors in this syndrome more pertinently than Bramwell,[13] who stated:

> It is suggested . . . that recurrent and periodic ocular paralysis and ophthalmoplegic migraine are probably always syndromes of vascular origin; that the ocular paralysis is due to pressure upon the nerve either (*a*) by a leaking aneurysm

11. Alpers, B. J., and Schlezinger, N. S.: Aneurysm of the Posterior Communicating Artery, Arch. Ophth. **42**:353 (Oct.) 1949.

12. Jaeger, R.: Aneurysm of the Intracranial Carotid Artery, J. A. M. A. **142**:304 (Feb. 4) 1950.

13. Bramwell, E.: The Etiology of Recurrent Ocular Paralysis (Including Periodic Ocular Paralysis and Ophthalmoplegic Migraine), Edinburgh M. J. **40**:209, 1933.

or (*b*) by an aneurysm that is still intact or an artery which has an abnormal relationship to the nerve; in the latter case, symptoms result when the aneurysm or artery which lies in contact with the nerve is temporarily distended as a result of vasomotor changes such as accompany an attack of migraine.

Sunderland [14] gave an excellent anatomic review of the vascular arrangement at the base of the brain and its relation to the cranial nerves, which emphasized the close relation of these structures. From such a study it is easy to understand the reactions in nerves which are possible as a result of physiologic and pathologic changes in the vessels.

Ocular signs and headache are common in all cases of intracranial aneurysm, but they are particularly common in cases of lesions affecting the intracranial part of the carotid artery before it branches into the middle and the anterior cerebral artery; also involved may be the two rather constant anterior choroidal and posterior communicating arteries. Within a radius of about 1 inch (2.54 cm.) around this section of the carotid artery lie the optic, oculomotor, trochlear, abducens and trigeminal nerves; any one nerve or all may be involved at times in lesions of these vessels. The oculomotor nerve, being more closely adjacent to the carotid artery, is the nerve most commonly damaged by aneurysm of the artery—hence, the early oculomotor paralysis. The same location is abundantly supplied for pain sensation by tiny branches from the ophthalmic division of the fifth cranial nerve, and any pressure or irritation causes excruciating pain, which is projected to the eye socket and the forehead and often along the side of the nose. Thus, one has an obvious cause for the common symptoms of paralysis of the third nerve with ocular and unilateral head pain.

Jaeger [13] treated 20 of 31 patients by craniotomy and direct attack on the lesion; three procedures were employed: (1) ligature of the neck of the aneurysm; (2) ligature of the carotid artery on either side of the aneurysm, and (3) in 2 cases, covering of the aneurysm with a thin layer of cotton to serve in the formation of a new fibrotic covering to reenforce its wall. Five of the 20 patients died, an operative mortality of 25 per cent. The author stated the belief that theoretically all the deaths might have been avoided and that no death resulted from operative shock or uncontrollable hemorrhage. In all other patients the unilateral frontal headache was completely cured; since this was the predominant affliction, its relief was gratifying. Also of interest was the recovery of function of the third, fourth and sixth nerves after operation. The author stated that nerves seriously damaged by pressure may gradually recover complete function within a period

14. Sunderland, S.: Neurovascular Relations and Anomalies at the Base of the Brain, J. Neurol., Neurosurg. & Psychiat. **11**:243, 1948.

ranging from one week to a year. There is not complete agreement with this statement.

The syndrome, then, of persistent frontal or orbital pain associated with paralysis or paresis of the third nerve occurring usually in an adult should be suspected of being due to aneurysm of the intracranial portion of the carotid artery. Arteriography and surgical treatment are the procedures proposed.

COMMENT

All these rather clearcut syndromes have previously been classified under the head of migraine, and one now sees that one by one, slowly and gradually, certain definite entities have been more accurately described and classified. It is within the realm of possibility that ultimately the term migraine may be restricted to a much more clearly defined condition, with a more precise understanding of its cause and effect. With increased powers of diagnosis, coupled with the evolution of research and further refinements in clinical and laboratory observations, it is entirely conceivable that migraine, which is now merely a name applied to a symptom complex of unknown etiology, may become obsolete.

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Clinical Notes

A NEW INSTRUMENT FOR LAMELLAR KERATOPLASTY

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WHEREAS perforating keratoplasty is becoming a common operation both in the United States and in Europe and gives satisfactory results in the hands of experienced ophthalmic surgeons, lamellar keratoplasty is not very popular in the New World. The experiences of my colleagues and myself with the latter operation are, however, so encouraging that I wish to draw attention to its wide field of indication and, in particular, to a new instrument which we have designed to facilitate the taking of the lamellar graft. We believe that this improvement of technic is to a great extent responsible for the satisfactory results we obtain.

It is an interesting fact that lamellar keratoplasty is often able to induce a clearing up of the surrounding opaque corneal tissue. Filatow [1] (1937) therefore proposed it as a preliminary operation in cases of extensive corneal leukoma in which he later wanted to perform a perforating keratoplasty, and as a means of clearing up a graft which had turned opaque after the critical period of twenty days. This trophic and therapeutic action (tissue therapy) of the lamellar graft is a most interesting feature, and one which we observed in some of our cases. Besides the optical indications for lamellar keratoplasty in cases of mainly superficial opacities of the cornea (superficial form of Groenouw's familial nodular dystrophy, primary edema and fatty degeneration of the cornea, postinflammatory superficial opacities of the cornea seriously interfering with vision and band keratitis) a lamellar graft is often the only therapeutic measure which can check recurring scrofulous or metaherpetic keratitis or a torpid corneal ulcer (Mooren's ulcer or rodent ulcer of the cornea). In these cases the operation may be performed during the acute inflammatory stage (Paufique, Sourdille and Offret [2]; Paufique [3]; Sourdille [4]; Coppez [5]; Franceschetti and Doret [6]), with surprisingly good results. In a case of recurring pterygium it may also be the method of choice. This operation is also gaining importance in cases of chemical burns of the cornea. Thus, the indications for lamellar keratoplasty are wide, and are ever increasing, particularly with the encouraging results obtained in inflammatory diseases of the cornea.

From the University Eye Clinic of Geneva; Director, Prof. A. Franceschetti

1. Filatow, V. P.: Vestnik oftal. **10**:635, 1937.
2. Paufique, L.; Sourdille, G. P., and Offret, G.: Les greffes de la cornée, Masson & Cie, Paris, 1948.
3. Paufique, L.: Bull. et mém. Soc. franç. d'opht. **69**: 210, 1949.
4. Sourdille, G. P.: Bull. et mém. Soc. franç. d'opht. **69**:214, 1949.
5. Coppez, L.: Ann. d'ocul. **182**:597, 1949.
6. Franceschetti, A., and Doret, M., in the proceedings of Société Suisse d'ophtalmologie, Fribourg, October 1949.

Although we have had no chance as yet to perform a lamellar keratoplasty in a case of trachomatous pannus, we believe that it would be of value in this dreadful complication of trachoma.

Lamellar keratoplasty is not a difficult operation and is certainly much less dangerous than the perforating one, simply because the eyeball is not opened. It is now made still easier and safer by the use of our new knife for the removal of the lamellar graft from the donor. This step in the operation has always been a delicate procedure. After the trephine marking is made, one ordinarily tries to cut a disk of corneal tissue by dissecting as deeply as possible with a small hockey knife held parallel to the surface. It is evident that parallel splitting of the corneal lamellas is difficult, as the flat hockey knife has to be constantly adjusted to the double curvature of the cornea.[7] Since cuts of the cornea parallel to its lamellas heal with much fainter opacification than those which run obliquely or vertically, it is highly desirable to obtain a regular and parallel incision of the fibers. With the hockey knife, which cuts bit by bit, it is almost impossible to obtain such a result. Furthermore, in this procedure, one has to hold the graft with a hook, threads or forceps, and the

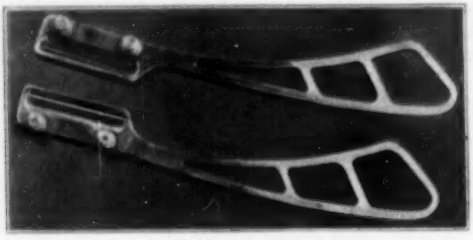

Fig. 1.—The instrument.

trauma thus caused cannot be disregarded. Although the graft is said to be resistant to mechanical trauma, it is certainly desirable to touch it as little as possible.

REMOVAL OF LAMELLAR GRAFT

The Instrument.—Our instrument (fig. 1) consists of half a razor blade fixed in such a way that a thin bar runs parallel with, and a short distance in front of, and above, its cutting edge.[7a] The relative position of the bar and the blade has been established empirically. The bar serves to press the cornea flat, while the blade immediately following it automatically produces an even, smooth cut—the principle of Tiersch's transplantation applied to the cornea.

The taking of the graft with the new instrument is so easy that it is possible to obtain lamellar grafts directly from the donor's eyes. This may prove of great advantage, particularly in countries where it is difficult to obtain permission to enucleate the eye for the purpose of performing a keratoplasty. I am thinking mainly of the countries of the Far East, where the necessity of keratoplasty also arises much more frequently (trachoma, corneal ulcers) than in western

7. Paufique, Sourdille and Offret,[2] p. 160.

7a. A. Canossa, technician of the clinic, cooperated in making the instrument.

countries. No layman will notice that a superficial graft has been removed from the cadaver's eye, and this will make it much easier to get the permission to take it.

I shall describe first the technic of removal of the transplant from the cadaver's eye in position, practicable for grafts up to a diameter of 7 to 8 mm. Larger grafts must be cut on the enucleated eye, a procedure which I shall describe later.

Preparation.—We take the graft as soon as possible, at the latest, two hours after death. The cadaver's eyes are prepared in the same fashion as for an aseptic operation: The area is washed with soap and water; tincture of iodine and alcohol are used for the skin, and the conjunctival sac is irrigated with sterile isotonic sodium chloride solution. The area is covered by a sterile towel with a hole. The surgeon's hands are prepared as usual; if this cannot be done in the room where the graft is taken, he wears sterile gloves.

Fixation.—After insertion of a lid retractor, strong silk sutures are passed through both the superior and the lateral rectus muscles. The ends of each suture are tied together to form a loop which can easily be held with one finger. Since it is necessary to increase the tension of the eye in order to make a regular, clean cut, saline solution is injected into the eyeball. For this purpose we use a 2 cc. syringe with a needle 3 cm. long and not too pointed. The sclera is pierced in the upper temporal quadrant about 8 mm. behind the limbus, the needle pointing in the direction of the center of the eyeball. Once the point of the needle is in the vitreous, saline solution is slowly injected until a definite resistance is felt. Usually 0.5 cc. is sufficient to bring the tension up to 50 or 60 mm. of mercury, which is optimal for the incision. Then the needle is pushed through the sclera of the opposite side and is left in position to block the holes. This, together with the two muscle sutures, gives an ideal fixation of the eyeball. In this way, the eye may be lifted should the supraorbital margin interfere with the knife at the beginning of the incision.

Trephining.—The next step (fig. 2) is a trephine incision of the desired size and depth. Great care must be taken not to perforate the globe. It must always be remembered that the normal cornea is only 0.5 to 0.6 mm. thick (in the cadaver slightly more), and the depth of the cutting part of the Franceschetti trephine must be adjusted accordingly.

Lamellar Incision.—The knife is then applied, being directed always from above and from the temporal side of each eye (two symmetric knives are therefore necessary, one for the left and one for the right eye). The proximal end of the bar is slightly pressed on the cornea, and the blade begins to cut at some distance peripheral to the trephine incision, so that the incision will be in the deeper layers by the time the area of the graft is reached. The knife is then drawn slowly and gently to the side, with constant mild pressure exerted on the bar. Usually when about half the length of the blade has been used, the neat circular corneal disk will lie on the blade (fig. 3). It is evident that the larger the graft desired, the more one must press on the cornea with the bar while cutting. The part flattened should always be somewhat larger than the part of the graft being cut; otherwise the edges of the graft will be thinner, and a graft of even thickness is desired.

Transfer of the Graft to a Special Container with Holofusin.[8]—While the larger lamellar grafts resume their normal curvature immediately after being cut (fig. 4), one may sometimes confuse the epithelial side with the cut surface in the very small grafts (e. g., those of 3 mm. diameter). The latter,

8. Paufique, Sourdille and Offret,[3] p. 73.

therefore, we place between two watch glasses movable along a central vertical rod (fig. 5) with the epithelial side of the graft downward. The two watch glasses leave only a space of about 1 mm. between them, so that the graft will remain in the position in which it has been placed even after it is dipped in holofusin (modified Tyrode solution). The container with the graft is then kept in the refrigerator at + 4 C. until the time of operation.

Fig. 2.—Fixation of the globe with sutures through the superior and lateral rectus muscles. Isotonic sodium chloride solution has been injected into the eyeball, and the trephine incision is being made.

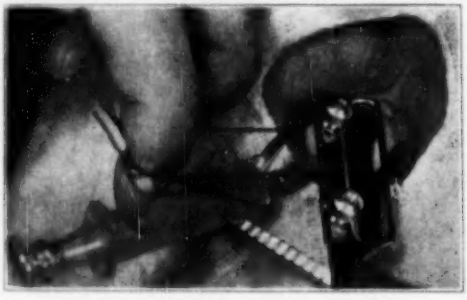

Fig. 3.—Lamellar incision completed. The disk of corneal tissue lies on the blade.

For the removal of a total lamellar graft, it is advisable to enucleate the eyeball. This must be done under aseptic conditions—if possible, not later than twelve hours after death, provided the cadaver has been kept in the refrigerator. Since the tension in cadaver eyes is low, we have found it most convenient to fix the eyeball with eight to ten needles on a large cork stopper, the center of which has been slightly hollowed out (fig. 6). By inserting the needles close

Fig. 4.—The large lamellar graft resumes its normal curvature immediately after the incision is terminated. For better demonstration, a small cardboard has been placed beneath the graft.

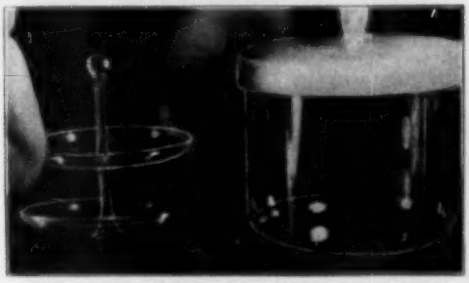

Fig. 5.—Container for transfer of small lamellar grafts.

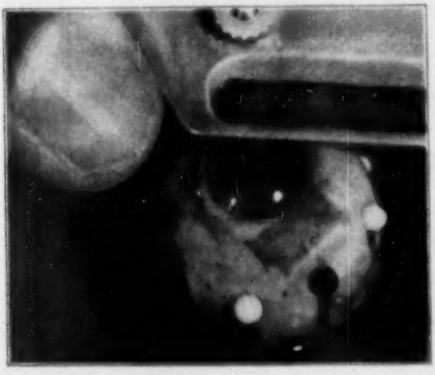

Fig. 6.—Fixation of the enucleated eyeball on a cork stopper with needles. The knife is applied. (No trephine incision was made in this case.)

to the eyeball, one can increase its tension to the level at which the lamellar incision is best performed. In this way the tension will also remain constant during the incision. The heads of the needles are pushed in so that they will not interfere with the knife, which is now applied 1 mm. outside the limbus. The incision is performed as previously described. It should be possible to complete it with a single horizontal movement in one direction (fig. 7). The amount of pressure to be here applied by the guiding bar and the slight tilting necessary in following the curvature of the cornea are easily determined by practicing the incision a few times. If the blade is not very sharp, and this may be true even

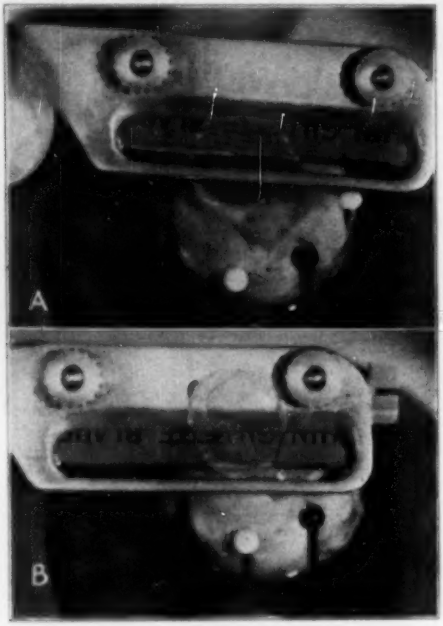

Fig. 7.—The incision. Here it has been terminated before three fourths of the length of the blade has been used.

of a new blade, one to and fro movement may be necessary to complete the incision. We prefer to do the trephining after the lamellar incision, but it may also be done before. We stop our lamellar incision a short distance from the limbus (fig. 7 *B*), withdraw the knife, spread the graft back on the remaining cornea and fix it with two forceps on the border at 2 and 10 o'clock, respectively. This fixation at three points will be sufficient to avoid deformation during the trephine incision (10 mm. diameter). The advantage of doing it in this way is that one need not be afraid of perforation and can go deep into the cornea. If the trephining is done before the lamellar incision, perforation must be avoided, for obvious reasons. For large, total lamellar grafts the trephining is not necessary.

If the incision is well made, it will include the whole limbus, and the graft will be fairly round, well curved and easily adjusted to a bed previously prepared in the patient's cornea with the same instrument or with a hockey knife. A few stitches at the border will keep it in position. For the smaller lamellar grafts (6 to 7 mm.) we use double-armed crossed sutures inserted at the limbus (Franceschetti and Doret [9]). It goes without saying that the smaller grafts are easier to take from the enucleated eye and may preferably be obtained in this way whenever possible.

SUMMARY

The wide field of indication for lamellar keratoplasty and the increasing importance of the procedure are stressed. A simple instrument is described by which the taking of lamellar grafts is greatly facilitated and the trauma to the transplant reduced to a minimum. The principle underlying the action of this instrument consists in flattening the cornea by a bar just in front of the cutting edge of a razor blade. The technic is described.

9. Franceschetti, A., and Doret, M.: Bull. et mém. Soc. franç. d'opht. **59**:83, 1946.

Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

Review of the Literature

IRVING H. LEOPOLD, M.D.
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ANTIBIOTICS AND CHEMOTHERAPY

CONSIDERABLE literature in the past year has been devoted to observations concerning antibiotics. There are now available for clinical and experimental use the following antibiotics: penicillin, streptomycin, dihydrostreptomycin, tyrothricin, bacitracin, neomycin, polymyxin, aureomycin, chloramphenicol (chloromycetin®) and terramycin. New antibiotics are being discovered, studied and made available in great numbers.[1]

On the basis of experimental data and clinical trials, systemic dosage schedules have been suggested. (See tables derived from literature available during past year.[2]) Because of the nature of the blood-aqueous

From the Department of Ophthalmology, University of Pennsylvania.

1. Arriagada, A.; Savage, M. C.; Abraham, E. P.; Heatley, N. G., and Sharp, A. E.: Ayflivin (Antibiotic Produced by a Particular Strain of Bacillus Likenformis), Brit. J. Exper. Path. **31**:425, 1950. Arriagada, A.; Florey, H. W.; Jennings, M. A., and Walmark, T. G.: Biological Observations on Ayflivin, ibid. **31**:58, 1950. Newton, G. G. F.: Antibiotics from a Strain of Bacillus Subtilis, ibid. **33**:306, 1950. Asheshov, I. N.; Strelitz, S., and Hall, E. A.: Antibiotics Active Against Bacterial Viruses, ibid. **30**:175, 1949. Barnes, E. M.: Laterosporin, A. and Laterosporin, B.: Antibiotics Produced by B. Laterosporus, ibid. **31**:100, 1950. Gill-Carey, D.: Antibiotics from Aspergilli, ibid. **31**:114, 1950. Gardner, J. F.: An Antibiotic Produced by Staphylococcus Aureus, ibid. **31**:30, 1950. Waksman, S. A., and Lechevalier, H. A.: Neomycin, Science **109**:305, 1949. Finlay, A. C.: Terramycin, ibid. **111**:85, 1950. Schoenbach, E. B.; Bryer, M. S., and Long, P.: Clinical Use of Polymxin, Ann. New York Acad. Sc. **51**:987, 1949.

2. (*a*) Hollander, L., and Hardy, S. M.: The Use of Aureomycin Ointment in Dermatology, Am. Practitioner **1**:54, 1950. (*b*) Long, P. H., and others: The Experimental and Clinical Use of Polymyxin, Chloromycetin, and Aureomycin, California & West. Med. **70**:157, 1949. (*c*) Woodward, T. E.; Parker, R. T., and Hall, H. E.: Therapeutic Results with Aureomycin and Chloramphenicol, Bull. New York Acad. Med **26**:66, 1950. (*d*) Horsfall, F. L., Jr.: Advances in Diagnosis of Virus Infections, ibid. **26**:3, 1950. (*e*) Brainerd, H.; Bruyn, H. B.; Meiklejohn, G., and Scaparone, N.: Assay of Aureomycin in Body Fluids, Proc. Soc. Exper. Biol. & Med. **70**:318, 1949. (*f*) Brainerd, H.: The Proper Use of Chemotherapeutic Agents, Am. Practitioner **4**:226, 1949. (*g*) Bellows, J. G., in Streptomycin, edited by S. A. Waksman, Baltimore, Williams & Wilkins Company, 1949, chap. 38. (*h*) Keefer, C. S.: Dosage

barrier, therapy of ocular infections cannot be based on dosage schedules satisfactory for other body tissues and fluids. One must be certain that the drug employed will reach an effective concentration in the infected tissue. Therefore, studies on ocular penetration by the various methods of administration with each of these antibiotics are important. For the

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(Footnote continued on next page)

same reason, trials with varying dosages and routes of administration against standard experimental infections and clinical trials are necessary.

The ophthalmologist must also be aware of the toxic symptoms of each drug, for other tissues of the body as well as the ocular structures.

Penetration and toxicity studies for penicillin, streptomycin and tyrothricin have been reported before 1949.

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During 1948, 1949 and 1950 such data have appeared for bacitracin,[3a', b'] aureomycin [3c', d'] and chloramphenicol (chloromycetin®).[3e'] The results of penetration studies from these various reports are summarized in tables 1 to 4. Older drugs are included for comparison. Several facts are evident:

1. Although only a few drugs penetrated through the normal cornea (sulfonamides, chloramphenicol), all penetrated readily when the epithelial barrier was removed by ulceration or abrasion.

2. Iontophoresis increased penetration through the normal cornea. In many of these eyes, but not all, some evidence of damage to the corneal epithelium was evident after iontophoresis. Dyson [3f'] has shown that the barrier properties of the epithelium are impaired by the iontophoretic procedure. The impaired permeability thus would seem not only to permit the ions to move by diffusional processes, owing to

TABLE 1.—*Penetration into Aqueous Humor* After Instillation into the Cul-de-Sac*

Drug	Normal Cornea	Abraded Cornea
Sulfanilamide	+	+++
Sulfadiazine sodium, 10%	+	+++
Sulfamethazine sodium, 10%	++	+++
Sulfamerazine sodium, 10%	+	+++
Sulfacetimide sodium, 10%	+	+++
Penicillin sodium, 250-2,000 units/cc.	±	++
Bacitracin, 500-1,000 units/cc.	±	++
Streptomycin hydrochloride, 5,000 micrograms/cc.	±	++
Aureomycin borate hydrochloride, 0.5%	—	++
Chloramphenicol 0.25% (2,500 micrograms/cc.)	+	++

* — indicates none; ±, poor; +, fair; ++, good; +++, very good.

their kinetic motion, but in the presence of continued iontophoresis to enable them to cross at an accelerated pace a previously nonconducting barrier. This helps to explain the favorable effect of cathode iontophoresis on substances that theoretically would respond to anode

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iontophoresis, e. g., streptomycin [28f] and aureomycin.[2cf, df] The reversal of poles probably limits the penetration of these drugs, but it is necessitated by the fact that anode iontophoresis is more harmful to the cornea.[28f]

TABLE 2.—*Penetration into Normal Rabbit Eye After Intramuscular Administration*

	Aqueous Humor	Vitreous Humor	Cornea	Sclera	Ocular Muscle	Conjunctiva	Choriocapillaris	Optic Nerve	Lens	Iris
Penicillin										
4,000 units/Kg	−	−	−	−	+	+	−	−	−	−
100,000 units/Kg	+	±	+	+	+	++	+	±	−	++
Streptomycin										
10,000 micrograms/Kg	+	−	−	+	+	+	−	−	−	−
100,000 micrograms/Kg	++	+	±	+	++	++	+	±	−	++
Aureomycin										
20,000 micrograms/Kg	−	−	−	−	..	..	−	..	−	−

TABLE 3.—*Intraocular Penetration in Normal Rabbit Eye After Intravenous Administration*

	Aqueous Humor	Vitreous Humor	Cornea	Sclera	Anterior Uvea	Posterior Uvea	Ocular Muscle	Conjunctiva	Optic Nerve	Lens
Penicillin										
4,000 units/Kg	±	−	−	−	−	−	±	+	−	−
25,000-100,000 units/Kg	++	±	+	+	+	±	+	++	+	−
Streptomycin										
10,000 micrograms/Kg	+	−	−	+	±	−	+	+	−	−
100,000 micrograms/Kg	++	+	+	+	++	+	+	++	+	−
Aureomycin										
20,000 micrograms/Kg	+	±	++	++	++	++	..	++	..	−
Chloramphenicol										
50,000 micrograms/Kg	++	+	+	+	++	+	+	++	±	−
100,000 micrograms/Kg	++	++	++	++	++	+	+	++	+	−

TABLE 4.—*Penetration into Aqueous and Vitreous Humor After Oral Administration*

	Aqueous Humor	Vitreous Humor
Aureomycin		
50 mg./Kg	−	−
Chloramphenicol		
100 mg./Kg	++	+

3. Corneal bath technics increased penetration of almost all drugs through the normal cornea, but deRoetth and Bellows and associates [2cf, df] did not find an increase for aureomycin by this method.

4. Detergents also increased the penetration of some drugs through the intact cornea.[26f] It is well known that detergents enhance the penetration of drugs locally applied.[21f-1f] Ginsburg and Robson [21f] suggest

that detergents increase penetration into the cornea by an effect on the corneal epithelium, possibly by solubilizing the intercellular cement. These authors also call attention to the mild adverse effects of detergents on the corneal epithelium, as has previously been described by Swan [28m] and Leopold.[28o]

5. Subconjunctival injection of antibiotics increased the amounts of intraocular penetration for all antibiotics over that obtained by instillation of the ointment or drops in the presence of a normal cornea. For aureomycin [2c, 4] and chloramphenicol,[2e] this method was found to be irritating. Very much higher levels in the aqueous humor were obtained with chloramphenicol in propylene glycol than in water by this method, but the injections were more irritating.[2e]

All these drugs will produce local hypersensitivity in susceptible persons. In improper concentration, all will damage the corneal epithelium on instillation and the intraocular structures on injection. Sensitivity to one antibiotic, fortunately, does not mean sensitivity to another. Local sensitivity to streptomycin did not indicate sensitivity to dihydrostreptomycin.

ADMINISTRATION

The proper drug for any individual infection should be selected by virtue of bacteriologic sensitivity tests run against the responsible organisms.

Marginal Blepharitis.—Solutions and ointments may be used. Solutions should be applied to the lid margins by painting or soaking with saturated cotton pledgets after removal of crusts. This should be done at least four to five times daily. Ointments may be applied three to four times daily, alone or combined with solution therapy. Ointment bases will usually afford better penetration when they are oil in water types, although water in oil types persist longer.[2e] When a medicament is placed in the cul-de-sac, the distribution of the drug between the vehicle and the tissue is generally in accordance with the relative affinities of the drug for the vehicle and for the tissue.[2g]

Conjunctivitis.—Instillation of drops every fifteen minutes for two hours, and then every hour for twenty-four to forty-eight hours, combined with use of an ointment during sleep, will usually suffice. Therapy should be continued for forty-eight hours after all signs of infection have disappeared, to prevent recurrence.

Dacryocystitis.—Instillations are made five times daily, together with direct injection into the lacrimal sac daily.

Acute Keratoconjunctivitis.—The schedule is the same as that for conjunctivitis.

Superficial Injuries to the Eyes.—For such injuries, e. g., corneal abrasions and chemical burns, instillation every two hours will usually suffice to prevent secondary infection.

Deep Keratitis.—Local therapy may be combined with systemic therapy. One may use corneal baths with solutions advised for iontophoresis. Baths may be applied for thirty to sixty minutes twice daily. Iontophoresis and subconjunctival injection may be employed.

TABLE 5.—*Administration of Antibiotics in Ocular Infections*

Drug	Concentration
Solutions for Local Use	
Penicillin	1,000-10,000 units/cc.
Streptomycin; dihydrostreptomycin	5,000 micrograms/cc.
Bacitracin	1,000 units/cc.
Aureomycin	5 mg./cc.
Chloramphenicol (chloromycetin*)	2.5 mg./cc.
Sulfacetimide sodium	0.3 Gm./cc.
Sulfamyloo* †	0.01 Gm./cc.
Sulfadiazine sodium	0.1 Gm./cc.
Ointments	
Penicillin	1,000 to 50,000 units/gram of ointment vehicle (higher concentrations may be used with crystalline penicillin)
Streptomycin; dihydrostreptomycin	5,000 to 10,000 micrograms/gram of vehicle
Bacitracin	500 to 1,000 units/gram of vehicle
Aureomycin	5 mg. +/gram of vehicle
Chloramphenicol	2.5 mg. +/gram of vehicle
Sulfadiazine	0.05 Gm./gram of vehicle
Sulfacetimide sodium	0.1 Gm./gram of vehicle
Solution for Iontophoresis	
	As above; usually cathode pole on corneal electrode; 3 milliamperes for 2 to 3 min.
Subconjunctival Injection	
Penicillin	50,000 units/0.5 cc. water or 0.25 cc. of 1:1,000 epinephrine hydrochloride and 0.25 cc. of water (can use 0.25 cc. of 2% procaine hydrochloride)
Crystalline penicillin	1,000,000 units/0.25 cc. of 1:1,000 epinephrine hydrochloride + 0.75 cc. water
Streptomycin; dihydrostreptomycin	10,000-20,000 micrograms/0.5 cc. water, or as above
Aureomycin	2.5 mg/0.5 cc. water
Chloramphenicol	1.2 mg./0.5 cc. water or 25 mg./0.5 cc. of propylene glycol

* Registered trade name.
† Sulfamyloo* is 4-(aminomethyl)-benzene sulfonamide hydrochloride.

Other Conditions.—For intraocular infections, anterior and posterior uveitis, postoperative infections, optic neuritis, cavernous sinus thrombosis and orbital cellulitis a combination of systemic and ocular injections may be required. The more overwhelming the infection, the more heroic the therapy must be.

Mode of Action.—Antibiotics may be divided into those that destroy both bacteria and animal cells and those that act specifically on bacteria.[7a,7]

Penicillin and streptomycin are examples of antibiotics which damage specifically bacteria, in that they have a rather low toxicity for animal cells and a high toxicity for bacteria, whereas a drug such as actino-

TABLE 6.—*Dosage of Antibiotics for Systemic Administration*

Drug	Concentration	Method
Penicillin	(1) 50,000-100,000 units every 3 hr., aqueous solution	Intramuscular
	(2) 200,000 units every 12 hr., crystalline in aqueous solution	Intramuscular
	(3) 300,000 units every 12 hr., oily or aqueous suspension	Intramuscular
	(4) 300,000 units, procaine complex in oil with 2% aluminum monostearate every 48 hr.	Intramuscular
	(5) 5,000,000 units daily	Continuous intramuscular or intravenous drip*
	(6) 100,000 units every 3 hr.	Oral
Streptomycin; dihydrostreptomycin	1 to 2 Gm. daily; divided doses	Intramuscular
Aureomycin†	(1) 25 to 50 mg./Kg. body weight, initial dose 50 mg./Kg. body weight—daily dose, subsequently divided into 4 doses (approximately 1.0 to 1.5 Gm. stat. and 0.5 Gm. every 6 hr. thereafter)	Oral
	(2) 0.5 mg./Kg., initial dose 15 mg./Kg. in divided daily doses, usually every 8 hr.	Intravenous
Chloramphenicol	60 mg./Kg. body weight, initial dose 30-60 mg./Kg. body weight, maintenance dose daily Average dose 2 Gm. stat., 0.5 Gm. every 4 hr. subsequently	Oral Intravenous preparation soon available

* The penicillin is dissolved in 1 to 2 liters of isotonic sodium chloride solution or glucose solution; 50 mg. heparin is added to prevent thrombophlebitis at site of administration. As much as 200,000,000 units daily has been given in this fashion.

† This drug is best tolerated when taken on a full stomach or with aluminum hydroxide gels. It is irritating and poorly absorbed when given intramuscularly.

TABLE 7.—*Doses Tolerated by Intraocular Injections*

Anterior chamber or vitreous chamber	Penicillin	1,000-5,000 units/cc. of water
	Streptomycin; dihydrostreptomycin	1,000 micrograms/0.1 cc. of water
	Bacitracin	10-100 units/0.1 cc. of water
	Aureomycin	50-250 micrograms/0.1 cc. of water
	Chloramphenicol	250 micrograms/0.1 cc. of water

mycin, streptothricin or tyrocidin is a protoplasmic poison. The latter drugs appear to damage constituents which are common to many types of living cells, not bacteria only. It is obvious that antibiotics vary in their toxicity. Penicillin, for example, is harmful to some bacteria but not to all. Some antibiotics are harmful to a few animal cells and not to all. For example, gramicidin is highly injurious to rickettsias and to spermatozoa but has little toxicity for other animal cells, and

is known to act mainly against gram-positive bacteria. There is still a great deal that has to be learned concerning the mode of action of the various antibiotics.

TABLE 8.—*Susceptibility of Organisms to Various Antibiotics*

Organism	Antibiotic Recommended
Gram-positive cocci	Penicillin
Penicillin-resistant strains	1. Aureomycin or chloramphenicol 2. Bacitracin (local)
Gram-negative cocci	
Gonococcus	1. Penicillin 2. Aureomycin or chloramphenicol 3. Bacitracin (local)
Meningococcus	1. Sulfadiazine and sulfamerazine 2. Bacitracin (local)
Gram-positive rods	
Bacillus anthracis	1. Penicillin
Clostridia	2. Sulfadiazine and sulfamerazine Aureomycin or chloramphenicol (antibacterial therapy always secondary to antitoxin therapy)
Gram-negative rods	
Coli aerogenes group	1. Streptomycin, aureomycin or chloramphenicol
Typhoid-Salmonella group	1. Chloramphenicol 2. Aureomycin
Brucella	1. Chloramphenicol or aureomycin
Shigella	1. Sulfonamides or chloramphenicol or aureomycin
Hemophilus influenzae	1. Streptomycin or aureomycin or chloramphenicol
Hemophilus pertussis	1. Chloramphenicol 2. Aureomycin
Proteus vulgaris	1. Streptomycin or chloramphenicol
Pseudomonas aeruginosa	Polymyxin (but nephrotoxic), streptomycin, chloramphenicol, aureomycin, sulfonamides—all occasionally fail
Spirochetes	
Syphilis	1. Penicillin
Yaws	2. Aureomycin or chloramphenicol
Relapsing fever	3. Bacitracin (nephrotoxic)
Spirochetal jaundice	
Mycobacteria	
Tubercle bacillus	1. Streptomycin or dihydrostreptomycin in combination with paraaminosalicylic acid or promizole* or thiosemicarbazone
Rickettsiae	
Typhus	Chloramphenicol or aureomycin both superior to paraaminobenzoic acid
Murine typhus	
Tsutsugamushi fever (scrub typhus)	
Rocky Mountain spotted fever	
Q fever	
Viruses	
Psittacosis	Penicillin, chloramphenicol, aureomycin
Lymphogranuloma venereum	Aureomycin or chloramphenicol
Trachoma	Sulfonamides, penicillin, chloramphenicol, aureomycin
Inclusion blennorrhea	Sulfonamides
Atypical pneumonia	Chloramphenicol or aureomycin

* Registered trade name.

In the volume on antibiotics cited [28] there are listed at least 40 antibiotics which come from fungi, and these do not include the ones that have been derived from Basidiomycetes. An example of substances which belong in this group is penicillin. Seventeen antibiotics derived

from the Basidiomycetes are listed in this volume, examples of which are sparassol and hirsutic acid. Twenty antibiotics are listed as coming from Actinomyces, of which examples are streptomycin, actinomycin, chloramphenicol and aureomycin. Approximately 20 antibiotics are derived from bacteria, of which gramicidin and bacitracin are examples, and the authors list 25 antibiotics derived from seed plants, an example of which is dicumarol (3-3′-methylenebis-[4-hydroxycoumarin]). There are still others which have been derived from lichens and algae. It is evident, therefore, that there are innumerable antibiotics which have been only partially investigated. Many others will undoubtedly be discovered and investigated in the near future.

The task of the ophthalmologist, as of other physicians, will be considerable if he conscientiously tries to employ antibiotics in treatment of ocular infestions. It will be necessary to have close association with bacteriologic facilities, so that he may be informed not only as to the etiologic factor in any particular ocular infection, but also as to the sensitivity of the organism to the various types of antibiotics. In this way, he may properly choose the specific antibiotic. The ophthalmologist must also consider the toxicity to the drug, the sensitivity of the patient to the drug, the cost of the drug and the route of administration. For example, aureomycin and chloramphenicol have approximately the same theoretic field of activity against bacteria, rickettsias and some viruses. However, in about 50 per cent of patients aureomycin produces definite signs of gastrointestinal irritation.[2b,c] With chloramphenicol such signs are extremely rare. Ocular penetration levels show that chloramphenicol orally administered penetrates readily into the ocular tissues,[3e] whereas aureomycin penetrates poorly.[2a,c, b] Solutions of aureomycin, like those of many other antibiotics, are not very stable.[2a] Actually, aureomycin deteriorates in dilute solutions within forty-eight to seventy-two hours even under refrigeration. Chloramphenicol, on the other hand, in dilute solution is rather stable at room temperature.[3e]

For ophthalmic use, 25 mg. of aureomycin hydrochloride with sodium chloride and sodium borate provided in a vial is simply diluted with 5 cc. of distilled water.[2a] Aureomycin hydrochloride is very acid (p_H 2.9), and no satisfactory preparation for intramuscular use at present is available. However, the drug is available for intravenous use. Ten cubic centimeters of 2.6 per cent solution of leucine is added to an ampule containing 100 mg. of aureomycin hydrochloride. The proper dose of this freshly mixed solution is then injected intravenously over a period of at least five minutes.[2b,c]

Clinical results following aureomycin therapy have been reported in patients with Rocky Mountain spotted fever, various types of typhus,

primary atypical pneumonia, brucellosis, or undulant fever, various forms of ophthalmologic infections, infections of the urinary tract, lymphogranuloma venereum, as well as other diseases.[2o,r,k]

Chloromycetin,® or chloramphenicol, an antibiotic, produced by Streptomyces venezuelae, can be prepared synthetically.[2m,r,v] The present commercial preparation is a mixture of the synthetic and the biologic antibiotic. Although the original streptomycete was obtained from soil near Caracas, Venezuela, it has recently been discovered in the soil of Illinois.[2o]

Good clinical results have been obtained with chloramphenicol therapy in the treatment of Rocky Mountain spotted fever, typhus, tsutsugamushi fever, scrub typhus, typhoid, brucellosis, bacillary infections of the urinary tract, primary atypical pneumonia and tularemia.[2o] Chloramphenicol has been shown to be successful in the therapy of pertussis [2r] and brucellosis.[2p,q]

It is apparent that aureomycin has some effect in the early stages of syphilis.[2r]

DRUGS IN TREATMENT OF TUBERCULOSIS

Special attention should be paid to the use of streptomycin and other drugs in the treatment of ocular tuberculosis.[3]

Experience in Ocular Tuberculosis Therapy.—From the results of their research, Woods and his co-workers [3b, c] suggest the use of 0.5 Gm. of streptomycin administered intramuscularly every twelve hours and 6 Gm. of promizole® (4,2′-diaminophenyl-5′-thiazole sulfone) given orally in divided doses. The results in Woods's series were about the same with dihydrostreptomycin hydrochloride as with streptomycin. Satisfactory clinical results may be obtained with as little as 26 Gm.

3. (*a*) Grignolo, A.: Experimental and Clinical Results of Use of Streptomycin in Tuberculous Infections of the Eye, Minerva méd. **1**:16, 1948; Clinical Use of Streptomycin in Nontuberculous Infections of the Eye, ibid. **1**:271, 1948. (*b*) Kennedy, J. D.; Woods, A. C.; Buckley, J.; Berthrong, M., and Burky, E. L.: Experimental Studies of Ocular Tuberculosis: IX. Failure of Penicillin to Affect the Course of Experimental Ocular Tuberculosis, Arch. Ophth. **39**:261 (March) 1948. (*c*) Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. The Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, ibid. **39**:471 (April) 1948. (d) XI. Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit, ibid. **40**:1, (July) 1948. (*e*) Woods, A. C.: Therapeutic Action of Streptomycin and Promizole® in Clinical Ocular Tuberculosis: A Preliminary Report ibid. **42**:521 (Nov.) 1949. (*f*) Bietti, G. B.: Use of Paraaminosalicylic Acid Alone or in Association with Streptomycin in Ocular Tuberculosis, ibid. **43**:431 (March) 1950. (*g*) MacAskill, J., and Weatherall, M.: Streptomycin and Promanide in Experimental Ocular Tuberculosis, Brit. J. Ophth. **34**:147, 1950. (*h*) Woods, A. C.: Experimental Studies on the Pathogenesis and Treatment of Ocular Tuberculosis, ibid. **33**:197, 1949.

of streptomycin combined with 156 Gm. of promizole.[9] Woods suggests that it would be better to give a total dose of 42 Gm. of streptomycin and about 250 Gm. of promizole.[9] MacAskill and Weatherall[5g] were able to show some beneficial effect on experimental tuberculous lesions with the combined use of streptomycin and glucosulfone sodium ("promanide"; promine[9] [sodium p-p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate]). With their lesions they are unable to demonstrate any appreciable synergism between glucosulfone sodium and streptomycin. In none of their experimental animals was definitely established tuberculous infection of the eye eradicated.

Others,[4] from the clinical and experimental data, conclude that the combination of the paraaminosalicylic acid and streptomycin control ocular tuberculosis much better than the therapeutic agents hitherto employed. Bietti[4f] suggests several courses of paraaminosalicylic acid and streptomycin. Each course should extend over three weeks and can be repeated once or more. He advises the addition of iontophoresis for lesions of the anterior segment. Clinically, his patients received 10 to 12 Gm. of paraaminosalicylic acid daily, divided in four doses, for twenty days. In addition, they received 0.5 to 1 Gm. of streptomycin daily. Iontophoresis with paraaminosalicylate sodium in 5 per cent solution was carried out on several of his patients, with beneficial effect. Considerable difficulty is sometimes encountered in these experiments in obtaining a standard lesion.

Rees and Robson[5] and associates describe a standard tuberculous lesion of the cornea—a means for testing various antituberculous agents in vivo. This lesion consisted of a corneal infection made by injecting tubercle bacilli directly into the cornea of the anesthetized mouse. These investigators tried a streptomycin, paraaminosalicylate and "sulfetrone" (a diaminodiphenylsulfone derivative) with this standard technic and were able to demonstrate a better effect with a combined treatment with streptomycin and paraaminosalicylic acid than with all the other therapies tried.

Streptomycin in Treatment of General Tuberculosis.—In reviewing the current status of drug therapy in tuberculosis, the Committee on

4. Bietti.[4f] Witmer, R., and Ragaz, L.: Pharmacologic Data and First Results of Treatment of Tuberculous Conditions of the Eye with Paraaminosalicylic Acid, Schweiz. med. Wchnschr. **79**:452, 1949. Lepri, G., and Fornaro, L.: Paraaminosalicylic Acid in Experimental Ocular Tuberculosis, Arch. de ottal. **53**:8, 1949; Combination of Streptomycin and Paraaminosalicylic Acid in Experimental Ocular Tuberculosis, ibid. **53**:129, 1949. Mata, P.: Treatment of Ocular Tuberculosis with Antibiotics, Arch. Soc. oftal. hispano-am. **9**:415, 1949.

5. Rees, R. J. W., and Robson, J. M.: Experimental Tuberculous Infections of the Cornea of the Mouse, Brit. J. Pharmacol. **5**:77, 1950. Gardiner, P. A.; Rees, R. J. W., and Robson, J. M.: Intracorneal Infection as a Method for Testing Antituberculous Substances, ibid. **4**:209, 1949.

Medical Research and Therapy of the American Trudeau Society [6] states that the use of 1 Gm. of streptomycin daily or 1 to 2 Gm. of dihydrostreptomycin hydrochloride daily is the best compromise between the higher toxicity of higher daily doses and the lessened therapeutic efficiency of smaller daily doses for tuberculous conditions, with the exception of miliary tuberculosis and tuberculous meningitis. In these conditions they advise the use of 2 to 3 Gm. daily. They also suggest that one can reduce the rate of emergence of streptomycin-resistant tuberculous organisms in two ways: (1) by administering streptomycin at greater intervals or (2) by combining streptomycin with paraaminosalicylic acid. With use of the combination, therapy can be extended over a longer period. They recommend the use of streptomycin for forty-two to sixty days, when the drug is given alone, but when streptomycin is used in combination with paraaminosalicylic acid the treatment may be continued for ninety to one hundred and twenty days. A shorter period of treatment results in less resistant organisms but poorer therapeutic response. A longer course may result in more resistant organisms but has a better therapeutic response in the majority of cases. This committee also states the opinion that dihydrostreptomycin has no advantage over streptomycin with regard to therapeutic efficiency, nor is it established that it is as effective as streptomycin. Moreover, there has been no change in the rate of emergence of resistant organisms. However, vestibular disturbances, such as vertigo and ataxia, were definitely less with dihydrostreptomycin than with streptomycin. Deafness was either greater with dihydrostreptomycin or was the same as with streptomycin.

Tucker [7] has shown that a daily dose of 2 Gm. of streptomycin is superior to 1 Gm. for both extrapulmonary and pulmonary tuberculosis. However, the advantages of the larger dose are offset by the toxicity. Reduction of the daily dose from 2 to 1 Gm. has decreased the toxicity without much change in clinical effectiveness, but reduction to 0.5 Gm. daily did reduce the effectiveness.

It is exceedingly interesting to learn that patients with ocular tuberculosis benefit from streptomycin therapy. The dose is such that one would not expect to find adequate concentration in normal eyes, but might in the presence of infection.[5a] Apparently, this small dose—1 Gm. daily—allows sufficient penetration in the presence of inflammation to produce clinical results. However, in tuberculosis meningitis, with which there has been more clinical experience than with ocular

6. Tucker, W. B.; Fellows, H. H.; Gale, J. W.; Jenkins, D. E.; Kirby, M. M. W.; Lincoln, E. M.; Schwartz, J. H., and Trumble, H. G.: Current Status of Drug Therapy in Tuberculosis, Am. Rev. Tuberc. **61**:436, 1950.

7. Tucker, W. B.: Evaluation of Streptomycin Regimens in Treatment of Tuberculosis, Am. Rev. Tuberc. **60**:715, 1949.

tuberculosis, there is still a feeling that systemic therapy should be reenforced by direct intrathecal or intracisternal injection of streptomycin because of the nature of the blood-cerebrospinal fluid barrier.[8]

In an effort to explain why large doses of antibiotics and longer intervals work as well as smaller doses and shorter intervals, Ungar [9] measured the concentration of penicillin in tissue exudates. He found that penicillin remained longer in tissue exudates than in the blood stream.

Paraaminosalicylic Acid in Tuberculosis Therapy.—Paraaminosalicylic acid was introduced into medicine by Lehmann in 1945. It was shown to be bacteriostatic against the tubercle bacillus in vitro and in vivo, and it is well tolerated in therapeutically effective doses. However, it is less effective than streptomycin. It has an antipyretic action but no influence on the results of the Mantoux test. It is relatively nontoxic but can produce hemorrhages when in high concentration in the blood stream. It may deplete the serum potassium. It often produces signs of gastrointestinal irritation, and a few instances of damage to the liver have been detected. The committee of the American Trudeau Society [6] recommends the use of 3 Gm. four times a day. They suggest that the drug be prepared in solution: 60 Gm. of sodium bicarbonate and 100 Gm. of paraaminosalicylic acid made up in water to a volume of 500 cc. The solution should be placed in a vessel large enough to permit effervescence. Five cubic centimeters of this solution will equal 1 Gm. of paraaminosalicylic acid. This solution rapidly deteriorates, so that it can be used only for forty-eight hours, and it must be refrigerated during this interval. The drug seems to be more effective when combined with streptomycin, and it definitely has value in cases in which the organisms have developed a resistance to streptomycin.[6]

Thiosemicarbazone in Tuberculosis.—A thiosemicarbazone (4-acetylaminobenzaldehyde thiosemicarbazone), known in Germany as "conteben," and for which the proprietary names "tibione" and "myvizone" have been proposed, has been reported on by Hinshaw and McDermott [10]; Behnesch, Mietzsch and Schmidt [11]; Domagk [12] (the

8. Streptomycin in the Treatment of Tuberculosis, editorial, J. A. M. A. **142**:654 (March 4) 1950.

9. Ungar, J.: Penicillin in Tissue Exudates After Injection; Journal-Lancet **258**:56, 1950.

10. Hinshaw, H. C., and McDermott, W.: Report to Clinical Sub-Committee on Thiosemicarbazone, Am. Rev. Tuberc. **61**:145, 1950.

11. Behnesch, R.; Mietzsch, F., and Schmidt, A.: Chemical Studies on Thiosemicarbazone. Am. Rev. Tuberc. **61**:1, 1950.

12. Domagk, G.: Investigation on the Anti-Tuberculous Activity of Thiosemicarzabone, Am. Rev. Tuberc. **61**:8, 1950.

original investigator); Mertens and Bunge [13] and others.[14] According to Mertens and Bunge,[13] the thiosemicarbazones have a definite beneficial effect on clinical tuberculosis. The more labile the lesions and the better the blood supply, the greater was the effect of thiosemicarbazone therapy. The best results were obtained in a mucous membrane type of tuberculosis. Although treatment must be individualized, an average dose of the drug of 2 mg. per kilogram of body weight may be given orally. The drug does have some toxicity in that it produces exanthems, which are frequently preceded by moderately severe conjunctivitis. Many patients complain of gastrointestinal irritation, and several instances of anemia and granulocytosis have been reported. Thiosemicarbazones are less effective than streptomycin but perhaps have a greater tuberculostatic effect than that of paraaminosalicylic acid.

SULFONAMIDES

New sulfonamides are still being investigated. Gantrisan[9] (3,4-dimethyl-5-sulfanilamide-isoxazole) is an example.[15] Combinations of sulfonamides, e. g., sulfadiazine, sulfamerazine, sulfacetimide and sulfamethazine (N'-[4,6-dimethyl-2-pyrimidyl]-sulfanilamide), are more effective and less toxic than individual sulfonamides.[16] Other investigators have reconsidered the problem of intraocular penetration of sulfonamides.[17]

MISCELLANEOUS DRUGS

Urea in 25 per cent solution applied as a corneal bath appears to have some merit in the treatment of dendritic ulcer when combined with local use of atropine, instillation of soft paraffin ointment and bandaging.[18]

Attention should be called to the revival of bacteriophage and bacterial filtrates in therapy of infection. Kravitz [19] tried phages and filtrates in cases of external ocular infections, with good results.

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13. Mertens, A., and Bunge, R.: The Present Status of Chemotherapy of Tuberculosis with Conteben, Am. Rev. Tuberc. **61**:20, 1950.

14. Current Status of Chemotherapy of Tuberculosis of Man: Report to the Council on Pharmacy and Chemistry, J. A. M. A. **142**:650 (March 4) 1950.

15. Rhoads, P. S.; Svec, F. A., and Rohr, J. H.: Clinical Evaluation of a New Sulfonamide, Quart. Bull., Northwestern Univ. M. School **28**:104, 1949. Svec, F. A.; Rhoads, P. S.; Rohr, J. H., and Kraus, L.: A New Sulfonamide, Arch. Int. Med. **85**:83 (Jan.) 1950.

16. Johnson, P. B.: Studies on Absorption, Excretion and Toxicity of Sulfonamide Mixture, South. M. J. **42**:761, 1949.

17. Davson, H.: The Penetration of Some Sulfonamides into the Intraocular Fluids, J. Physiol. **110**:46, 1949. Sorsby, A.: Concentration in the Aqueous of Various Sulfonamides After Systemic Administration, Brit. J. Ophth. **33**:347, 1949.

18. Klein, M., and Miller, S. J. H.: Local Application of Urea for the Treatment of Dendritic Ulcer, Brit. J. Ophth. **33**:643, 1949.

19. Kravitz, D.: Treatment of Local Lid Infections with Phages and Particularly with Filtrates, Am. J. Ophth. **32**:1047 (Aug.) 1949.

OCULAR REACTIONS TO SURGICAL MATERIAL

Gurtler reports 20 cases in which cotton wool threads were observed in the anterior chamber. In these cases no disturbance of healing occurred. There was a mild secondary reaction for a short period in a few eyes.[20]

A case of talc granuloma at the insertions of the horizontal rectus muscles fourteen years after surgical treatment of a squint is described.[21] The condition clinically resembles keloid, sarcoid or lymphoblastoma. Biopsy revealed epithelial cells embedded into connective tissue together with a few multinucleated giant cells.

Tissue reactions occur from waxes derived from spool cotton and may be responsible for some of the untoward effects (granuloma) following the use of cotton as sutures. It is advisable to extract these waxes with an innocuous solvent before using.[22]

HYALURONIDASE AND HYALURONIC ACID

Pirie [23] found that the intraocular injection of hyaluronidase caused a prolonged inflammatory reaction in the eye. This confirmed the earlier observations of von Sallmann.[24] Within two hours after this enzyme was injected into the anterior chamber there appeared a prolonged inflammatory reaction, requiring about twenty-four hours for its appearance after injection of the enzyme into the vitreous humor.

It was also found that the hyaluronic acid is disaggregated after such injection. However, some time after subsidence of inflammation, the hyaluronic acid in the vitreous humor is again in the viscous aggregated condition. The return to normal of the hyaluronic acid of the vitreous humor probably shows a production of hyaluronic acid as a continuous process in the living eye. Meyer [25] has already suggested that hyaluronic acid is constantly produced and removed from the eye, and Pirie's experiments give some proof for this by showing that in the living animal hyaluronic acid is gradually replaced in a viscous aggregated form after

20. Gurtler, E.: Threads of Cotton in the Anterior Chamber After Intraocular Operations, Wien. klin. Wchnschr. **61**:686, 1949.

21. McCormick, G. L.; Macaulay, W. L., and Miller, G. E.: Talc Granulomas of the Eye, Am. J. Ophth. **32**:1252, 1949.

22. Rosenberg, N.; Moallen, S., and Vroman, L.: Tissue Reactions to Waxes Derived from Spool Cotton, Am. J. Surg. **60**:363, 1950.

23. Pirie, A.: The Effect of Hyaluronidase Injection on the Vitreous Humor of the Rabbit, Brit. J. Ophth. **33**:678, 1949.

24. von Sallmann, L.: Absorption from the Vitreous, Am. J. Ophth. **31**:90, 1948; Experimental Studies on Vitreous: I. Experiments on Diffusion in the Vitreous and on Permeability of Its Surface Condensation Layer, Arch. Ophth. **42**:583 (May) 1949.

25. Meyer, K.: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335, 1947.

it has been hydrolyzed by injected hyaluronidase. A fall in intraocular pressure was also noted for as long as three to four days after a single intravitreal injection of hyaluronidase.

Lynn and Ozment [26] also found that hyaluronidase produced considerable inflammation when injected into the anterior chamber of rabbits. The changes noted were clouding of the cornea, bulging of the cornea and iritis. Histologic studies of enucleated eyes revealed the destruction of corneal stroma with massive corneal edema, iritis and congestion of the ciliary processes. When hyaluronidase was instilled into the anterior chamber of 2 patients with secondary glaucoma, a temporary beneficial effect on the intraocular pressure was observed. It is interesting that the injections into the anterior chamber of human eyes did not produce the same evidence of inflammatory reaction. In neither patient was any corneal change noted. In 1 patient some changes in the iris of a mild nature were observed.

In a discussion of this paper, Dr. Paul W. Miles mentioned unpublished data presented by William E. Moore and Philip Shehan at the meeting of the Midwest Section of the Association for Research in Ophthalmology, Inc., at St. Louis, May 1948. The latter workers tried hyaluronidase in treatment of glaucoma, with favorable results in 4 patients. Moore and Shehan suggested that the chief effect of hyaluronidase is not the change in viscosity of the aqueous, but the alteration in the permeability of the cell membrane or the tissue barriers in the angle. They were able to demonstrate a more rapid disappearance of the india ink from the anterior chamber of eyes after the injection of hyaluronidase than from eyes in which this enzyme was not used. Other investigators [27] have reported on the ability of hyaluronidase to increase the permeability of membranes, particularly of the lens capsule.

Other studies [28] suggested that the ciliary processes contained hyaluronic acid, which in these experiments could be replaced by a sulfated mucopolysaccharide after repeated injections of testicular extract (hyaluronidase).

Hyaluronidase has been found to facilitate the passage of fluids into the tissues.[29] It has been shown to increase the diffusion of anesthetic

26. Lynn, J. G., Jr., and Ozment, T. L.: Some Effects of Injection of Hyaluronidase into the Anterior Chamber, Am. J. Ophth. **33**:33 (Jan.) 1950.

27. Seifter, J.; Fitch, D. R.; Baeder, D. H., and Begany, A. J.: The Action of Hyaluronidase and Steroids on Membrane Permeability, Am. J. M. Sc. **219**:346, 1950.

28. MacDonald, R. K.: Effects of Testicular Extract on Certain Ocular Structures, Am. J. Ophth. **32** (no. 6; pt. 2):96 (June) 1949.

29. Jaworski, A. A., and Farley, J. E.: Hyaluronidase in Administration of Fluids, J. Pediat. **79**:59, 1950.

agents and, at the same time, to decrease the duration of these agents.[30] This effect has been applied in ophthalmology, with similar conclusions; that is, there was greater and more rapid diffusion of the anesthetic solution. The onset of the anesthesia was more rapid than when the anesthetic was used without hyaluronidase. However, it was felt that the duration was about the same. The area of the anesthesia was greater with hyaluronidase incorporated in the solution, and the akinesia of the orbicularis and the extraocular muscles was more effective.[31] The dose recommended by Atkinson was a 2 per cent procaine hydrochloride solution with 0.4 per cent potassium sulfate. One drop of epinephrine hydrochloride (1:1,000) and 30 turbidity-reducing units of hyaluronidase (hydase®) should be added to each 5 cc. of anesthetic solution.

It has been observed that a serum inhibitor of hyaluronidase occurs in animals after surgical procedures.[32] A definite decrease in the spreading effect of hyaluronidase when injected cutaneously was found after such procedures. Testosterone propionate, estradiol benzoate, progesterone, pregnenolone and desoxycorticosterone when injected did not alter the spreading effect of hyaluronidase. Compound E (cortisone; 17-hydroxy-11-dehydrocorticosterone) and, to less extent, compound A did not inhibit the spread of intradermally injected hyaluronidase with india ink.[33]

Localized myxedematous areas have been shown to possess increased hyaluronic acid and chondroitinsulfuric acid.[34]

Godtfredsen [35] presents a new concept of the pathogenesis of retinal detachment. Mayer and Kull [36] show that an allergic tissue reaction will produce hyaluronidase, which, by its influence on tissue hyaluronic acid, facilitates the spread of edema. They also demonstrate that antihistamine

30. Kirby, C. H.: Eckenhoff, J. E., and Looby, J. P.: The Use of Hyaluronidase with Local Anesthetic Agents in Nerve Block and Infiltration Anesthesia, Surgery **25**:101, 1949.

31. Atkinson, W. S.: Use of Hyaluronidase with Local Anesthesia in Ophthalmology, Arch. Ophth. **42**:628 (Nov.) 1949.

32. Cole, J. W.; Shaw, D. T., and Fraser, P.: Wound Healing, Surg., Gynec. & Obst. **90**:269, 1950.

33. Opsahl, R.: The Role of Certain Steroids, Yale J. Biol. & Med. **21**:255, and 487, 1949; **22**:115, 1949.

34. Curtis, A. C.; Cawley, E. P., and Johnwick, E.: Association of Progressive (Malignant) Exophthalmos and Localized Myxedema, Arch. Dermat. & Syph. **60**:318 (Sept.) 1949. Wilson, E. M., and Pearce, R. H.: Mucopolysaccharide Content of the Skin in Localized (Pretibial) Myxedema, Am. J. Clin. Path. **19**:442, 1949.

35. Godtfredsen, E.: Investigations in Hyaluronic Acid and Hyaluronidase in the Subretinal Fluid in Retinal Detachment, Brit. J. Ophth. **33**:721, 1949.

36. Mayer, R. L., and Kull, F. C.: Influence of Pyribenzamine and Antistine upon the Action of Hyaluronidase, Proc. Soc. Exper. Biol. & Med. **66**:392, 1947.

drugs may inhibit the activity of hyaluronidase. Godtfredsen suggests that a local angioneurotic edema of the retina may occur. This leads to liberation of hyaluronidase. The localized retinal edema leads to local ischemia and cystoid degeneration, which goes on to rupture. The liberated hyaluronidase then depolymerizes the hyaluronic acid in the adjacent vitreous, reducing the viscosity of the vitreous humor. The hyaluronic acid then moves into the subretinal space. Perhaps antihistamine substances may serve as adjunct therapy in cases of retinal detachment, tending to block the activity of the hyaluronidase.

SOLUTION STERILITY

It has been suggested that benzalkonium (zephiran®) chloride U. S. P., 1 to 5,000, be used as a vehicle for solutions to be locally instilled into the eye.[37] Incompatible substances are mild silver protein U. S. P. (argyrol®), boric acid, sodium fluorescein, silver nitrate and other nitrates, as well as salicylate radicals.

Autoclaving may be used for sterilization of ophthalmic solutions.[38] Physostigmine salicylate does not stand autoclaving, while other drugs, e. g., cocaine and pilocarpine, lose some potency on repeated autoclaving.

ANTICHOLINESTERASE DRUGS

Investigations with diisopropyl fluorophosphate (DFP) in the past year confirm the earlier observations showing that this is an effective and useful drug in the medical therapy of glaucoma.[39] In mild cases of chronic glaucoma or wide angle glaucoma, diisopropyl fluorophosphate is effective in concentrations as low as 0.005 per cent. In the weak concentrations the drug has few, if any, undesirable effects, and even in this dilute concentration it will maintain a steadier daily tension curve than that shown by other miotics. It has also been demonstrated that when the drug is used in higher concentrations, such as 0.2 per cent, a larger number of patients are treated effectively. Of 150 glaucomatous eyes, Stone [39b] found that diisopropyl fluorophosphate in 0.2 per cent concentration would control the intraocular pressure in 90 over varying

37. McPherson, S. D., Jr., and Wood, R. M.: Self-Sterilizing Ophthalmic Solutions, Am. J. Ophth. **32**:675, 1949. Hughson, D. R., and Styron, N. C.: The Use of Alkyl-Dimethyl-Benzyl Ammonium Chloride for Maintenance of Sterility in Solutions, ibid. **32** (no. 6; pt. 2):102 (June) 1949.

38. Morrison, W. H., and Truhlsen, S. M.: Autoclaving of Drugs for Surgical Use, Am. J. Ophth. **33**:357, 1950.

39. (*a*) Raiford, M. B.: Clinical Evaluation of D. F. P. in Glaucoma Therapy, Am. J. Ophth. **32**:1399, 1949. (*b*) Stone, W. C.: Use of Di-Isopropyl Fluorophosphate (DFP) in Treatment of Glaucoma, Arch. Ophth. **43**:36 (Jan.) 1950. (*c*) Weinstein, P.: Glaucoma Treatment by Furmethide and Di-Isopropyl Fluorophosphate (D.F.P.), Ophthalmologica **118**:76, 1949. (*d*) Chlouser, G. R.: Diisopropyl Fluorophosphate (DFP) in Treatment of Glaucoma, Vestnik oftal. **28**:13, 1949. (*e*) Herain, V. J.: Neoglaucit, a New Miotic, Cesk. ofth. **5**:14, 1949.

periods of observation when previous miotics or surgical therapy had failed. The types of glaucoma benefited by this treatment were chronic and acute noncongestive glaucoma, chronic and acute congestive glaucoma and secondary glaucoma of various types, especially aphakic glaucoma. The complications encountered are similar to those previously reported; namely, ciliary spasm, false myopia, headache and brow ache and an occasional rise in intraocular pressure. This increase in tension occurred in 16 per cent of Stone's series. This incidence is higher than that for any previously reported group but is probably related to the fact that he used a 0.2 per cent concentration, whereas in earlier series the concentration was limited to 0.1 per cent.[40] It was apparent that the drug was more effective when higher concentrations were used, but, as would be expected, the complications were greater. It is important to note that in none of the 150 eyes treated by Stone was retinal detachment observed, and that with a concentration of 0.2 per cent the pain due to ciliary spasm gradually decreased after a few days of treatment.

It is evident from these studies that the conclusions drawn formerly for any miotic are applicable to diisopropyl fluorophosphate; namely, one should use the weakest concentration which is effective in the particular case involved, and the least number of instillations should be employed which will maintain a satisfactory intraocular pressure. If a weak concentration, such as 0.005 or 0.01 per cent, does not prove effective, we learn from Stone's work that 0.2 per cent concentration can be used with very little danger of undesirable effects.

Dunphy [41] has shown that diisopropyl fluorophosphate will produce miosis when instilled in complete darkness in a dark-adapted eye. This is not evidence that the drug constricts the pupil by direct action, but probably corroborates the belief generally held by pharmacologists that acetylcholine is constantly being formed at all parasympathetic nerve endings as a result of normal muscle tonus.

Grant [42] has shown that tetraethyl pyrophosphate will lower intraocular pressure in glaucomatous eyes. Tetraethyl pyrophosphate forms an irreversible combination with cholinesterase. Its action is comparable to that of diisopropyl fluorophosphate, but is not as long lasting. It will lower intraocular pressure which has been controlled previously by other miotics in their usual recommended concentration, and in

40. (*a*) Leopold, I. H., and Comroe, J. H.: Use of Diisopropyl Fluorophosphate in Treatment of Glaucoma, Arch. Ophth. **36**: 1 (July) 1946. (*b*) Leopold, I. H., and McDonald, P. R.: Di-Isopropyl Fluorophosphate (DFP) in Treatment of Glaucoma, ibid. **40**:176 (Aug.) 1948.

41. Dunphy, E. B.: Effect of Di-Isopropyl Fluorophosphate (D.F.P.) on the Pupil of the Dark-Adapted Eye, Am. J. Ophth. **32**:1404, 1949.

42. Grant, W. M.: Miotic and Antiglaucomatous Activity of Tetraethyl Pyrophosphate in Human Eyes, Arch. Ophth. **39**:579 (May) 1948.

some eyes will lower pressure not previously controlled. However, a large number of eyes acquire sensitivity to this drug. This will probably limit the practical value of tetraethyl pyrophosphate in glaucoma.

"Mintacol," a new synthetic organic phosphorus compound made by Bayer (E600) is also an anticholinesterase agent, closely related to diisopropyl fluorophosphate. It is an effective agent in lowering intraocular pressure when used in concentrations ranging from 1:5,000 to 1:10,000. A 1:10,000 solution has a stronger effect than that of physostigmine in the usual concentrations. In a normal eye, a 1:5,000 solution has no effect on the intraocular pressure. In a series of 60 glaucomatous eyes, 53 of which had chronic simple glaucoma or wide angle glaucoma, a 1:5,000 solution of "mintacol" had the same effect as a 2 per cent pilocarpine ointment. The experimenters with this drug recommend the use of a 1:7,000 solution.[43]

Koelle and Friedenwald [44] have devised a histochemical method for localizing cholinesterase activity in tissues. The substrate employed, acetylthiocholine, can be hydrolyzed by both specific and nonspecific cholinesterases; therefore the sites of both enzymes can be visualized. Koelle [45] has also shown that by using very dilute concentrations of diisopropyl fluorophosphate one can inhibit chiefly the nonspecific cholinesterase. Thus, one can separate by histochemical methods the two types of tissue cholinesterase.

MYASTHENIA GRAVIS

Because in the treatment of myasthenia gravis some anticholinesterase drugs have been more effective than others—for example, neostigmine as compared with physostigmine of equal anticholinesterase activity—the difference has been attributed to direct action of neostigmine on the muscle. Until recently, it has not been possible to distinguish between direct action and anticholinesterase action. With this introduction of anticholinesterase drugs, such as diisopropyl fluorophosphate and tetraethyl pyrophosphate, whose actions are irreversible, such analyses have been made. Studies have been made to determine whether anticholinesterase drugs act on skeletal muscle in one of two ways or in both; that is,

43. Glees, M., and Wüstenberg, W.: Experiences with "Mintacol" in the Normal and the Glaucomatous Eyes, Klin. Monatsbl. f. Augenh. **114**:455, 1949. Thiel, H.-L.: Experiments with a New Synthetic Miotic, "Mintacol," in Glaucoma, ibid. **114**:454, 1949.

44. Koelle, G. B., and Friedenwald, J. S.: The Histochemical Localization of Cholinesterase in Ocular Tissues, Am. J. Ophth. **33**:253, 1950.

45. Koelle, G. B.: Histochemical Localization of Cholinesterase in Ocular Tissues: Further Studies, presented at meeting of Wilmer Residents, Baltimore, April 1950.

whether they act only by inhibiting cholinesterase, and thus preserving acetylcholine, or whether they have a direct stimulating action on the end plate or the muscle fiber.[46]

Many investigators have shown that in the cat and frog neostigmine in suitable concentrations can produce a contraction of muscle after all the cholinesterase has apparently been inhibited by diisopropyl fluorophosphate. They have usually concluded that this indicates the direct action of neostigmine. However, it could also mean that diisopropyl fluorophosphate has not tied up all the cholinesterase.

It is evident from Hubbiger's experiments[46a] that carbamic esters, such as neostigmine and physostigmine, in low concentrations sensitized the frog's rectus muscle to acetylcholine by inhibition of cholinesterase. Neostigmine and physostigmine in concentrations well above those necessary for sensitization to acetylcholine appeared to have a direct stimulating effect on muscle. These drugs may also be considered as having an anticurare effect, which is due solely to inhibition of cholinesterase; that is, they allow enough acetylcholine to pile up so it can break through a curare block. However, after complete inhibition of cholinesterase by tetraethyl pyrophosphate, higher concentrations of the carbamic esters have a curarelike blocking action toward acetylcholine. In other words, anticholinesterase drugs may have several actions, depending on the concentrations and also on the sequence in which they are used. It has already been shown in the human eye that when diisopropyl fluorophosphate is used first, and physostigmine subsequently in the usual concentrations, an accumulative effect occurs, but when the drugs are used in the reverse order physostigmine will block the action of diisopropyl fluorophosphate.[46b]

Many drugs have been used in the therapy of myasthenia gravis[47]:

1. Ephedrine sulfate (10 to 30 mg. orally two or three times a day) has a slight effect, possibly by direct effect on muscle toxicity. The mechanism is not known.

2. Potassium ions (potassium chloride, 10-50 Gm. daily) are beneficial. Perhaps they facilitate production of acetylcholine.

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46. (*a*) Hubbiger, F.: The Action of Carbamic Esters and Tetraethylpyrophosphate on Normal and Curarized Frog Rectus Muscle, Brit. J. Pharmacol. **5**:37, 1950. (*b*) Riker, W. F., and Wescoe, W. C.: Direct Action of Prostigmine on Skeletal Muscle, J. Pharmacol. & Exper. Therap. **88**:58, 1946. (*c*) Miquel, O.: Action of Physostigmine, Di-Isopropyl Fluorophosphate and Other Parasympathomimetic Drugs on Rectus Muscle of Frog, ibid. **88**:67, 1946.

47. Stone, C. T., and Rider, A.: Therapy of Myasthenia Gravis,, J. A. M. A. **141**:107 (Sept. 10) 1949.

3. Guanidine hydrochloride (20 to 30 mg. per kilogram of body weight daily in three divided doses) helps in a few cases. Benefit seems to occur in patients with low creatinine excretion.

4. Thymectomy has helped about 50 per cent of patients so treated.

5. Neostigmine is the drug of choice. In most cases oral administration is satisfactory; some hypodermic administration is required. In crises it can be given intravenously as the methylsulfate in hourly doses. Usually 30 mg. in twenty-four hours is given, if needed.

6. Diisopropyl fluorophosphate is helpful, but results are not so dramatic as those of neostigmine. When given systemically, it has many disadvantages.

7. Hexaethyltetraphosphate, 10 to 12 mg. given intramuscularly every three to five days, is partially helpful.

8. Tetraethyl pyrophosphate was the most helpful of the strong anticholinesterase drugs. It has a more prolonged action than neostigmine and when carefully administered can be used in combination with neostigmine, in which case less neostigmine is required.

The last three drugs, as well as neostigmine, may produce muscular fasciculation, blurred vision, false myopia, spasm of the ciliary muscle, abdominal cramps, nausea, salivation, lacrimation, restlessness, bradycardia, and even convulsive seizures when used in excessive amounts. The margin of safety is not great, and therapy must be individualized.

9. The results with ACTH are discussed in the section on that drug.

It has been demonstrated that epinephrine will inhibit the hydrolysis of acetylcholine, methacholine (acetyl-beta-methylcholine) and benzyl choline by cholinesterase.[48] This may help to explain the favorable effect of the combination of epinephrine with cholinergic or anticholinesterase drugs in glaucoma.

No increase in cholinesterase content was demonstrable in the blood of patients during an induced allergic state. The histamine concentration also did not change.[49]

TISSUE THERAPY—FILATOV

Tissue therapy has been evaluated in the past year by trial in various ocular diseases. None of the reports shows the great enthusiasm originally registered by Filatov. However, many of the investigators feel that the therapy has some merit and that studies should be con-

48. Benson, W. M., and Meek, W. J.: Hydrolyses of Choline Esters in Presence of Adrenalin, Am. J. Physiol. **158**:327, 1949.

49. Hjort, A. M.; Worden, A. S., and Hogle: Evaluation of Histamine and Cholinesterase in Allergic Phenomena, Ann. Int. Med. **32**:217, 1950.

tinued.[50] The methods employ preserved and fresh placental and corneal tissue. When placental tissue was used in the fresh state, it was rendered aseptic with penicillin. When used in the preserved state, it was kept at low temperatures for seven days, as recommended by Filatov. Corneal implantations were taken aseptically from the eyes of cadavers, as for keratoplasty, and were kept at 4 degrees C. for eight days in a penicillin solution. The rationale of this therapy has not been elucidated satisfactorily.

In one report, surgical gut was inserted subconjunctivally for therapy of tuberculosis of the anterior segment, with favorable results.[50k] In one series of experiments it was found that tissue therapy would reduce and inhibit the effects of the pigmentary degeneration produced by sodium iodate.[50l]

The conditions in which tissue therapy has been tried include progressive myopia; recurring hemorrhages in the vitreous; retinitis pigmentosa; recurrent iridocyclitis; senile macular degeneration; various forms of keratitis, sclerokeratitis and keratoconjunctivitis, retinal detachments, and optic nerve atrophy.

Thorough investigations on this type of therapy have been reported in this country by Gordon [50n] and by Saltzman and Haig.[50o] These reports show no significant improvement that could be attributed to the therapy employed.

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50. (*a*) Durix, C.: Filatov's Tissue Therapy in Ophthalmology, monograph, Lyon, 1949. (*b*) Jebejian, R.: Tissue Therapy in Various Ocular Infections, Ann. d'ocul. **182**:658, 1949. (*c*) Bregeat, P.: Indications for the Subconjunctival Implantation of Fresh Placental Tissue, Bull. méd., Paris **63**:369, 1949. (*d*) Sourdille, G. P.: Special Indications and Contraindications for Tissue Therapy, Bull. Soc. d'ophth. Paris, **3**:550, 1949. (*e*) Grancini, C. L.: Experimental Anaphylaxis by Placenta, Prepared by Filatov's Method and Normal Placenta, Atti Cong. Soc. oftal. ital. **10**:448, 1948. (*f*) Kantorovich, A. Y.: Action of Tissue Therapy on Specific Sensitivity of Tuberculous Eye, Vestnik. oftal. **28**:329, 1949. (*g*) Arruga, H.: Usefulness of Comparison of Therapeutic Methods of the Two Eyes, Arch. Soc. oftal. hispano-am. **9**:349, 1949. (*h*) Averbuch, S. L.: Action of Tuberculin and of Subconjunctival Implantations of Catgut in Tuberculosis and Scrofula of the Eye, Vestnik oftal. **28**:3 and 26, 1949. (*i*) Bonavolonta, G., and Debaradinis, E.: Effects of Filatov's Tissue Therapy on Experimental Pigmentary Degeneration in the Rabbit, Boll. d'ocul. **28**:65, 1949. (*j*) Salvadori, L.: Tissue Therapy in Ophthalmology, Ann. ottal. e clin. ocul. **75**:101, 1949. (*k*) Weinstein, P., and Forgacs, J.: Experiences with Filatov's Tissue Therapy, Orvosi hetil. **90**:492, 1949. (*l*) Barraquer Moner, J. I.: First Impressions on Some Aspects of the New Tissues Therapy of Filatov, Arch. Soc. oftal. hispano-am. **9**:861, 1949. (*m*) Dehorter-Duez, C.: Results of Tissue Therapy, Bull. Soc. d'opht. Paris **1**:172, 1949. (*n*) Gordon, D. M.: Treatment of Retinitis Pigmentosa with Special Reference to Filatov's Method, Am. J. Ophth. **30**:656, 1947. (*o*) Saltzman, S. L., and Haig, C.: Treatment of Retinitis Pigmentosa with Cod Liver Oil Injections and Placental Implantation, Arch. Ophth. **43**:419 (March) 1950.

ANTIHISTAMINE DRUGS

Therapeutic benefit has been reported in various ocular diseases by administration locally and systemically of various antihistamine drugs.[51] Good results have been reported in the treatment of localized angioneurotic edema of the lids and conjunctiva, allergic conjunctivitis, contact dermatitis, eczema, vernal conjunctivitis, superficial keratitis and nodular episcleritis. The number of antihistamines is manifold, but they are very close in chemical and pharmacologic relation.[52]

It is now fairly well known that most of the toxic reactions of antihistamine drugs, such as drowsiness, are not serious, but there are case reports of profound effects on the central nervous system,[53] the genitourinary system[54] and the hemopoietic system.[55]

There is an increasing frequency of reports of hypersensitivity reactions to the antihistamine drugs themselves.[56] Of equal importance is the possible influence antihistamine drugs may have on skin testing.[57] There is some disagreement in the literature as to whether systemically administered antihistaminic drugs influence the cutaneous test with tuberculin. Most authors agree that the reaction is not altered.

There is a report in the Russian literature on the use of citral in treatment of glaucoma, suggesting that antihistamine substances may have some value in the therapy of glaucoma.[58]

Antihistamine drugs have been shown to have an anesthetic effect. This action has been investigated in experimental animals and shown

51. Grossmanz, E. E., and Loring, M. J.: Antistine in Nodular Episcleritis, Am. J. Ophth. **32**:1122, 1949. Nemeth, L.: Antihistamines in Ophthalmology, Brit. J. Ophth. **33**:665, 1949. Stocker, F. W.: The Use of Antihistaminic Drugs in Ophthalmology, South. M. J. **43**:242, 1950. Daily, R. E., and Daily, L., Jr.: Use of Privine-Antistine Drops in Ophthalmology, Am. J. Ophth. **32**:441, 1949.

52. Report of the Council on Pharmacy and Chemistry, J. A. M. A. **139**:377 (Feb. 5) 1949.

53. Rives, H. F.; Ward, B. B., and Hicks, M. L.: A Fatal Reaction to Methapyrilene (Thenylene), J. A. M. A. **140**:1022 (July 23) 1949.

54. Wolfson, S. A.: Urinary Obstruction Due to Tripelennamine Hydrochloride, J. A. M. A. **140**:958 (July 16) 1949.

55. Cahan, A. M.; Mielman, E., and Jacobson, B. M.: Agranulocytosis Following Pyribenzamine, New England J. Med. **241**:865, 1949

56. Epstein, E.: Dermatitis Due to Antihistaminic Agents, J. Invest. Dermat. **12**:151, 1949. Sherman, W. B., and Cooke, R. A.: Dermatitis Following Use of Pyribenzamine and Antistine, J. Allergy **21**:63, 1950. Mosko, M. M., and Peterson, W. L.: Sensitization to Antistine, J. Invest. Dermat. **14**:1, 1950.

57. Friedman, E.: Effect of Antihistaminication on the Tuberculin Reaction in Children, Am. Rev. Tuberc. **61**:442, 1950. Peck, S.; Finkler, B.; Mayer, G. G., and Michelfelder, T.: Effect of Various Modes of Administration of Pyribenzamine on the Histamine Wheal and Epidermal Sensitivity Reactions, J. Invest. Dermat. **14**:177, 1950.

58. Kemenskia, Z. A.: Use of Citral in Glaucoma, Sovet. Med. **9**:37, 1948.

to be present in the rabbit eye and in the human eye, but not to be deleterious when the drugs are used in recommended concentrations.[59]

Antihistamine drugs, locally and systemically administered, may overcome sensitivity to atropine so that atropine may be continued without deleterious effect.[60] Ross [61] and others [62] point out that systemically administered antihistamine substances may produce blurred vision, weakness of accommodation and possibly corneal edema.

Antistine® (2-phenylbenzylaminomethyl-imidazoline) in 0.5 per cent concentration is about as uncomfortable on instillation into the cul-de-sac as 0.5 per cent tetracaine hydrochloride. With higher concentrations (2 per cent) damage to the corneal epithelium can be demonstrated. With 0.5 per cent concentration Schlaegel [63] could not demonstrate any retardation of regeneration of the corneal epithelium, but higher concentrations were deleterious in this regard. Antistine® in this concentration does not affect the pupil. Other antihistamine drugs (diphenhydramine hydrochloride) have been shown previously to dilate the pupil.[64]

Systemically administered antihistamine drugs have been compared for their ability to overcome histamine introduced into the skin by iontophoresis.[65] This is one method of comparing their efficacy. Diphenhydramine (benadryl®), tripelennamine (pyribenzamine®) and pyrinisamine (neoantergan®; N-*p*-methoxybenzyl-N′,N′-dimethyl-N-α-pyridylethylene diamine) were not successful in this regard among the agents tested. However, the antihistamine drugs have actions other than their ability to overcome histamine. These other effects are anti-acetylcholinic local anesthetic, sympathomimetic, sympatholytic and antispasmodic. Some of the other agents may be superior in these actions.

59. Sheldon, J. M.; Lovell, R. G., and Kiess, R. D.: Observations on the Effect of Antihistaminic Compounds on the Corneal Reflex of Rabbits, Univ. Hosp. Bull., Ann Arbor **15**:42, 1949. Yonkmann, F. F.; Roth, F.; Smith, J.; Hansen, N., and Craver, B. N.: Local Anesthetic Properties of Antistine and Pyribenzamine Hydrochloride: Current Researches in Anesth. & Analg. **28**:170, 1949.

60. Fralick, F. B., and Kiess, R. D.: Use of Antihistaminic Drugs in Control of Atropine Dermatitis and Conjunctivitis, Arch. Ophth. **41**:583 (May) 1949.

61. Ross, J. V. M.: Some Ocular Effects of the Systemic Administration of Antihistaminics, Am. J. Ophth. **32**:987, 1949.

62. Waldriff, G. A.; Davis, J., and Lewis, G. M.: Antihistaminic Drugs in Dermatologic Therapy, Arch. Dermat. & Syph. **61**:361 (March) 1950.

63. Schlaegel, T. F., Jr.: Antistine—A Study of Its Toxicity, Am. J. Ophth. **32**:1088, 1949.

64. Harris, R.; McGavack, T. H., and Elias, H.: The Value of the Action of Dimethylaminoethyl Benzhydryl Ether Hydrochlorida (Benadryl), J. Lab. & Clin. Med. **31**:1148, 1946.

65. Sternberg, T. H.; Perry, D. J., and LeVan, P.: Antihistaminics, J. A. M. A. **142**:969 (April 1) 1950.

HEPARIN AND DICUMAROL*

Within the past year there have been many articles on anticoagulant therapy in medicine, surgery and ophthalmology.[66] In analyzing these data, it is well to keep in mind the steps in intravascular clotting:

1. Thrombocytes adhere to the intima of a blood vessel where the endothelium is damaged.

2. Thrombocytes pile up and some disintegrate, releasing thromboplastin.

3. In the presence of ionized calcium, thromboplastin converts inactive prothrombin to the active enzyme thrombin.

4. Small amounts of thrombin can be utilized by antithrombin.

5. Sufficient amounts of thrombin convert fibrinogen to fibrin.

6. Sufficient amounts of thrombin change the accelerator effect of globulin so that it increases the rate of liberation of thrombin.

7. Fibrin enmeshes other cells, such as the erythrocytes and leukocytes.

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66. (*a*) Riggs, D. S.: Anticoagulants, New England J. Med. **242**:179; (*b*) 216, 1950. (*c*) Nichols, E. S.: Chemical Use of Heparin and Dicumarol, New Orleans M. & S. J. **102**:208, 1949. (*d*) Smith, R. G.: Pharmacology of Anticoagulant Agents, ibid. **102**:159, 1949. (*e*) Anderson, G. M.: Treatment and Prevention of Pulmonary Embolism, Venous Thrombosis and Other Thrombo-Embolic Episodes, ibid. **102**:162, 1949. (*f*) McCann, J.: Thromboembolism, New England J. Med. **242**:203, 1950. (*g*) Müller, R.; Harvey, W. P., and Finch, C. A.: Antagonism of Dicumarol by Vitamin K Preparations, ibid. **242**:211, 1950. (*h*) Klien, B. A.: Prevention of Retinal Venous Occlusion, Am. J. Ophth. **33**:175, 1950. (*i*) Warner, E. D.; Brinkhaus, K. M., and Smith, H. P.: Quantitative Study on Blood Clotting, Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936. (*j*) Foley, W. T., and Wright, J. S.: Long Term Anticoagulant Therapy for Cardiovascular Diseases, Am. J. M. Sc. **217**:2136, 1949. (*k*) deTakats, G.: Anticoagulant Therapy, J. A. M. A. **142**:527, (Feb. 25) 1950. (*l*) Duff, J. F., and Shull, W. M.: Fatal Hemorrhage in Dicumarol Poisoning, ibid. **139**:762 (March 19) 1949. (*m*) Jublirer, R. A., and Glueck, H.: Capillary Fragility Studies on 100 Patients Receiving Dicumarol, J. Lab. & Clin. Med. **34**:448, 1949. (*n*) Weiss, W. D.; Coker, F. F., and Brambel, C. E.: Effectiveness of Dicumarol Prophylaxis Against Thromboembolic Complications Following Major Surgery: A Four Year Survey, 3304 Cases, Surg., Gynec. & Obst. **46**: 1949. (*o*) Allen, J. G.; Grossman, B. J.; Elghammer, R. M.; Moulder, P. B.; McKeen, L. L.; Jacobsen, L. D.; Pierce, M.; Smith, T. R., and Crosbie, J. M.: Abnormal Bleeding Response to Treatment with Toluidine Blue and Protamine Sulfate, J. A. M. A. **139**:1251 (April 30) 1949. (*p*) Powers, J. S., Jr.: Toxicity of Dicumarol, Ann. Int. Med. **32**:146, 1950. (*q*) McLean, J. M.: Anticoagulant Therapy in Retinal Vascular Occlusion: I. Tr. Am. Acad. Ophth. **53**:644, 1949. Puig Solanes, M.: Anticoagulant Therapy in Retinal Vascular Occlusion: II, ibid. **53**:649, 1949. (*r*) Pagliarani, N.; The Treatment of Thrombosis of the Retinal Veins by Anticoagulants, Gior. ital. oftal. **2**:335, 1949.

The factors that favor agglutination are (1) endothelial damage, (2) slowed circulation, (3) thrombocytosis and (4) change in plasma composition.

In table 19 are summarized some of the pertinent facts concerning heparin and dicumarol.[8]

It has been suggested that anticoagulant therapy be used as a preventive measure in retinal venous occlusion.[8a,b] For this purpose, ambula-

TABLE 9.—*Pertinent Data on Heparin and Dicumarol*[8]

	Heparin	Dicumarol
Structure	Polysaccharide of high molecular weight; related to chondroitinsulfuric acid and mucoitinsulfuric acid	Similar to vitamin K and salicylic acid
Characteristics	(Purple color with methylene blue) Acts rapidly for short time	Slow—maximum effect after one dose in 2 to 3 days later; effect may last 7 to 10 days
Source	Formed by mast cells; distributed in tissues near capillaries	Plants
Available form	100 units/mg. as sodium heparin, supplied in solution containing 10 mg./cc.	Tablets for oral use
Mode of action	Prevents prothrombin from changing to thrombin (will not dissolve clots already present)	Suppression of thrombin formation in liver (will not dissolve clots already present)
Antidotes	Basic substances; toluidine blue; protamine	Menadione vitamin K (50-100 mg.) injected intravenously; may be repeated every 2 hr.
Mode of administration	(*a*) 0.2 mg./cc. continuous intravenous in saline solution—14 mg./hr. (average pat.) or (*b*) Intermittent intravenous 50-150 mg. every 4 to 6 hr., total dose 400 mg. (*c*) Intramuscular injection as 10% aqueous solution; difficult to control amount absorbed	Initial dose 300 mg. orally; dose adjusted by estimation of daily prothrombin time; between 10 and 30% of normal prothrombin time aimed at; if prothrombin time greater than 30%, 100-200 mg. given; if prothrombin time less than 20% none given
Contraindications	(1) Hemorrhagic tendencies; (2) after cerebrovascular accident; (3) severe hypertension	Same as those for heparin, also liver disease

tory administration of dicumarol[8] is recommended. Therapy should be continued until there is clinical evidence of adequate collateral circulatory channels. In the cases observed by Klien an average of six months elapsed before clinical evidence of such channels appeared. In this therapy, Klien recommends starting with curative doses of dicumarol,[8] with reduction of the prothrombin level to approximately 25 per cent; in this phase of therapy the patient should always be hospitalized. It is perhaps better to start with heparin combined with dicumarol[8] and then gradually shift to dicumarol[8] for ambulatory therapy. While the patient is ambulatory, a prothrombin level of 50 per cent should be maintained. For measuring the prothrombin times, the method of Warner and

associates[66i] is recommended by Klien.[66h] She stresses the definite dangers with dicumarol® therapy but states the belief, as expressed in the literature,[66j] that with ordinary precautions ambulatory dicumarol® therapy does not hold any greater hazards than treatment in the hospital.

DeTakats,[66k] in a recent review of anticoagulants in surgery, also makes a plea for the use of anticoagulants in the prevention of thromboembolic phenomena. He notes that the treatment of acute thromboembolic phenomena requires massive doses of heparin, but that the doses are frequently insufficient, whereas the prophylactic use of anticoagulants requires far smaller doses. However, deTakats feels that dicumarol® is not as safe as intramuscularly administered heparin for prolonged anticoagulant therapy. With dicumarol® therapy, the spread of thrombi, pulmonary embolism and embolism of the peripheral arteries has been encountered with prothrombin levels between 50 and 30 per cent of normal.

Several problems are encountered in the administration of dicumarol® as an anticoagulant:

1. A standard procedure for determining and expressing prothrombin activity does not exist.

2. The correlation between the occurrence of hemorrhage and safe prothrombin levels is poor.

3. Thromboembolic phenomena appear in bedridden and ambulatory patients at prothrombin levels regarded as protective.

Dr. Albert Ochsner, in the discussion on deTakats' paper, stated that he had also been impressed with the difficulties in determining a safe prothrombin level in dicumarol® therapy and had observed patients with relatively low prothrombin values in whom thrombosis developed. He also called attention to the fact that venous thrombosis is dependent on a disproportion between prothrombin and antithrombin and that, of the two, antithrombin is probably the more important. Apparently, a deficiency of antithrombin facilitates clot development. If antithrombin deficiency is corrected by the administration of antithrombin, venous thrombosis may be prevented. He has been using alpha tocopherol (vitamin E), which is an efficient antithrombin, and has found that, provided it is administered before the decrease in antithrombin is too great, venous thrombosis can be prevented.

It is true that the majority of fatal hemorrhages due to dicumarol® poisoning are caused chiefly by gross overdosage. Nevertheless, of the 23 recently reported fatalities, at least 4 were within the so-called safe range of prothrombin levels.[66i] It has been shown also that capillary fragility is not the responsible factor in hemorrhage in cases of dicumarol® therapy.[66m] Nevertheless, there is evidence of the value of dicumarol® therapy, as cited by Weiss, Coker and Brambel.[66n]

The antidote for heparin is well known and is intravenously administered protamine sulfate; 1.5 mg. of this drug neutralizes the effect of 1 mg. of heparin. The action of protamine wears off in about four hours, and the injection may have to be repeated in certain hemorrhagic states.[66a]

For hemorrhage induced by dicumarol,[a] de Takats[66b] states that intravenous use of vitamin K and blood transfusions are the customary measure. He prefers 20 mg. doses of vitamin K given intravenously three times rather than one massive injection of 60 mg. In cases of hemorrhage due to heparin or dicumarol[a] transfusions are helpful.

McGuire[67] suggests the prolonged use of dicumarol[a] in glaucoma as a means of improving the visual field. He noted improvement in the visual fields of a number of eyes with long-standing glaucoma. This suggests that dicumarol[a] prevents thromboembolic phenomena in the nutrient vessels of the optic nerve. To date, these interesting results have been neither confirmed nor denied in the ophthalmic literature.

Bick and Haines[68] have undertaken a study of the penetration of heparin into the eye by various routes of administration, primarily with the hope that heparin may be used as a means of reducing postoperative scarring. They state that there is good experimental and theoretic evidence that heparin has a growth-retarding effect on fibroblasts. The most practical and certain method of heparinizing the eye is by the direct introduction of the drug. A pellet of heparin has been prepared which can be inserted subconjunctivally, and this apparently causes no undue reaction. Such implantation in the rabbit eye facilitated filtration from the anterior chamber into operative blebs after a type of iris inclusion. Apparently, heparin so placed interfered with the normal process of tissue repair.

Anaphylactic reaction may follow the injection of heparin.[69] This is another toxic sign which must be considered in the administration of this drug.

EFFECT OF RADIANT ENERGY ON THE EYE

An excellent review of the lesions of the eye from radiant energy is presented by Cogan.[70] The effects on the tissues of the eye are listed according to the individual structures:

67. McGuire, W. P.: The Effect of Dicumarol in the Visual Fields, in Glaucoma, Am. J. Ophth. **32**:1095, 1949.

68. Bick, M. W., and Haines, R. W.: Local Use of Heparin in the Eye, Am. J. Ophth. **32**:774, 1949.

69. Chernoff, A. I.: Anaphylactic Reaction Following the Injection of Heparin, New England J. Med. **242**:315, 1950.

70. Cogan, D. G.: Lesions of the Eye from Radiant Energy, J. A. M. A. **142**:145 (Jan. 21) 1950.

1. The eye as a whole. Glaucoma may follow sufficient roentgen irradiation of the eye. The glaucoma is usually preceded by uveitis.

2. Cornea. The cornea is selectively affected by the nonpenetrating forms of radiation, such as long infra-red, ultraviolet, grenz, beta or cathode rays. It is also affected by some of the penetrating radiations, such as roentgen and gamma rays.

The effects of infra-red radiation on the cornea are simply thermal burns with immediate onset, the opacification of the cornea resulting from coagulation of the corneal proteins. The effects of ultraviolet

TABLE 10.—*Transmission and Absorption of Radiant Energy in the Ocular Medium*

Wavelength	Ocular Effects
Long radiodiathermy waves	Transmitted through the eye readily; no appreciable absorption; therefore, little biologic effect
Short diathermy waves	Heat effects in eye; deleterious effect on anterior segment
Infra-red rays	
Long infra-red waves (longer than 2,000 millimicrons)	Rays absorbed by cornea and aqueous humor
Short infra-red waves (1,000 millimicrons)	Readily transmitted to the retina (iris pigment and retinal pigment absorb infra-red rays)
Visible rays	70% of rays of long, or red, end of the spectrum reach retina
	10% of rays of short, or violet, end of spectrum reach retina
Ultraviolet rays	
(Longer ultraviolet rays, 400 to 320 millimicrons)	Rays largely absorbed
(Shorter ultraviolet rays, 300 and less)	Rays chiefly absorbed by cornea
Grenz rays	90% of rays absorbed by cornea
Beta rays and cathode rays	Rays absorbed largely by cornea and conjunctiva but may penetrate as deep as 1 cm. into tissue
Roentgen rays	90% of rays reaches retina
Gamma rays and cosmic rays	Rays penetrate eye very well
Neutrons	High degree of penetration

radiation on the cornea consist predominantly of punctate erosions of the epithelium in the exposed areas. These symptoms appear after a latent period of five to twelve hours. Both these changes are usually superficial and seldom lead to permanent sequelae.

Grenz rays and beta (cathode) rays also produce superficial keratitis. The latent period may be a matter of days or weeks rather than hours. Repeated irradiation during the latent period has a cumulative effect. If the voltage is high enough, such as 25 kilovolts of grenz rays (soft roentgen rays) or up to several thousand kilovolts of beta rays (such as those emitted by radium), penetration of as much as 1 cm. may be expected, and there may be involvement not only of all the layers of the cornea but also of the lens.

Roentgen and gamma rays may also produce keratitis. The lag in development of the keratitis may be as long as several weeks after exposure. The deeper layers are more frequently involved than with the types of keratitis previously mentioned, and may actually lead to an intractable ulcer. Xerosis of the cornea and conjunctiva not infrequently follows, perhaps due to radiation atrophy of the lacrimal gland.

3. Lens. The lens may be affected by radiant energy, and this results in cataractous changes. The electric current may produce a cataract in many ways. The latent period may be as long as several

TABLE II.—*Radiant Energy*

A. Electromagnetic Radiation		B. Corpuscular Radiation (Subatomic Particles)	
Wavelength		Source	
Hundreds of meters	Radio waves	Artificial oscillators in radio stations; diathermy machines	
Thousands of millimicrons	Infra-red rays	Open furnaces; electric arcs; sun	
	Visible rays	Sun	
Hundreds of millimicrons	Ultraviolet rays	Welder's arc; quartz-mercury vapor lamp; sun	
	Grenz rays	Low voltage roentgen ray tube, 8-25 kilovolts	Electrons: Beta rays—radioactive substance Cathode rays—incandescent filavolt
	Roentgen rays	X-ray tubes—100-1,000 kilovolts	
	Gamma rays	Radioactive material (radium)	Neutrons: Unchanged portion of atomic nucleus released by disintegration of the atom (cyclotron)
Thousandths of microns	Cosmic rays	Interstellar space (atomic disintegration)	

years. This type of cataract characteristically begins in the anterior cortex and the anterior capsule.

Short diathermy waves may result in cataract, but it takes extreme intensities to do so.

When workers are near excessive heat and there is considerable infra-red radiation, cataract may be produced. Such cataracts result only from exposure to intense heat for many years. These cataracts are characteristically posterior cortical, with the formation first of saucer-like opacities, and belong to the so-called cataracta complicata. There may be a curled-up membrane on the lens in the pupillary area, due to the lamellar splitting of the anterior capsule.

It is questionable whether visible radiation actually ever produces cataract. There is little doubt, however, that ultraviolet radiation may cause profound changes in the lens if the rays reach the lens in sufficient

intensity. With grenz rays, ultraviolet rays and beta rays considerable corneal damage should result whenever the lens is also involved. Roentgen rays definitely produce cataract, and the susceptibility of the lens to roentgen rays is said to be an inverse function of age, most vulnerable being the fetus in utero. The latent period for development ranges from six months to twelve years. The cataract characteristically begins as an opacity in the posterior pole of the lens. It is sharply demarcated from the rest of the cortex, a feature which may help differentiate it from cataracta complicata. If the lesion is progressing, there may be vacuoles in the anterior cortex, and an anterior subcapsular haze may result. Cataracts from gamma rays and neutrons are similar to those produced by roentgen rays. The cataracts which may result from the atomic bomb are probably due to gamma rays and neutrons.

4. Retina. The retina may be damaged by infra-red and visible rays. These lesions are characteristically sharply demarcated. They most frequently occur after the viewing of an eclipse but may result from exposure to an artificial light source, such as a carbon arc. It is possible that nutritional factors may induce sensitization to visible radiations, so that retinal lesions may result from exposure to sunlight that is ordinarily innocuous. The ultraviolet rays probably produce no retinal damage. Roentgen and gamma rays are relatively without effect on nerve tissue. However, they can produce thickening of the arteries and chromatolysis of the ganglion cells, and it is possible that they produce vascular lesions in the retina

The only adequate form of therapy for the lesions of radiant energy seems to be prophylaxis.

IRRADIATION THERAPY

Most of the articles since April 1949 demonstrate the value of irradiation when properly managed in treatment of various ocular diseases, chiefly those of the anterior segment.[71] Pincus [72] reports the effect of radiation therapy on epithelial invasion of the anterior chamber after cataract extraction. Obviously, the best therapy is still prevention of

71. Strazzi, A.: X-Ray Therapy in Corneal Disease, Boll. d'ocul. **28**:267, 1949. Fedrizzi, G., and Ferri, L.: Roentgen Therapy of Superficial Ocular Diseases with Soft Rays, Atti Soc. oftal. ital. **10**:435, 1948. Alden, H. S.; Jones, J. W., and Rankin, J.: Roentgen Ray Treatment of the Eye: Further Experiences, Arch. Dermat. & Syph. **59**:430 (April) 1949. Mezey, P.: Ophthalmologic Application of Bucky Rays, Szemészet ophth. **86**:77, 1949. Swanberg, H.: Radium-D Ophthalmic Applicator Treatment Time, Mississippi Valley M. J. **71**:93, 1949.

72. Pincus, M. H.: Epithelium Invasion of Anterior Chamber Following Cataract Extraction, Arch. Ophth. **43**:509 (March) 1950.

epithelial downgrowth. But he does confirm the earlier results of Pirie and of Vail as to the value of irradiation in this condition.

Radiation therapy to prevent or destroy corneal vascularization depends on the production of obliterative endarteritis. Lenz[73] has found that three factors influence the outcome of treatment for prevention or obliteration of corneal vascularization by means of radiation therapy: (1) the condition of the cornea when treated, (2) the age of the capillaries and (3) the technic of the treatment.

Results are best when the opacity is due to infection, degeneration or trauma to the cornea. In approximately two thirds of the cases corneal vascularization may be prevented or obliterated. The results were better in cases in which therapy was instituted before any vessels were seen invading the cornea. Damage to blood vessels varied with the radiation dose, i. e., the amount of radiation reaching the vessel and the time in which it was administered. Damage is severer when the amount of radiation is great when the entire treatment is given in a single exposure. The injury is milder when the amount of irradiation is less and when the total dose is fractionated over several treatments. At first the total dose did not exceed 600 r. Later, however, Pincus raised this to 1,500 r. In none of these cases has cataract formation been noted to date. In the majority of cases the treatment consisted of a daily dose of 250 r, and this was repeated six times on consecutive days, until 1,500 r were applied. In the eyes with intense postoperative reactions smaller doses were used for the initial therapy.

A series of patients with pterygium, corneal opacities of vernal conjunctivitis and intense vascularization were treated with beta radiation, a radium-D applicator being used as the source of the beta rays.[74] The results were excellent in almost all cases, and in no case was there injury to the underlying or adjacent tissues.

Various methods have been worked out for applications of low penetrating radiation.[75]

Qualitative and quantitative differences with regard to biologic effects which may exist between beta and roentgen rays are not large, and the minor discrepancies that may be present are of little significance.[75a] Apparently, if one is aware of the limitations and necessary precautions, one can safely and effectively employ beta radiation from strontium or

73. Lenz, M.: Radiotherapy for the Prevention and Obliteration of Corneal Vascularization, Am. J. Ophth. (no. 3) (pt. 2) **33**:48, 1950.

74. Okrainetz, C. L.: Beta Irradiation of the Eye Using the Radium-D Applicator, Am. J. Ophth. (no. 3; pt. 2) **33**:52, 1950.

75. (*a*) Friedell, H. L.; Thomas, C. I., and Krohmer, J. S.: Beta-Ray Application to the Eye, Am. J. Ophth. **33**:525, 1950. (*b*) Wilson, F.: Beta Irradiation, ibid. **33**:539, 1950. (*c*) Scheie, H. G.; Dennis, R. H.; Ripple, R. C.; Calkins, L. L., and Buessler, J. A.: Effect of Low-Voltage Roentgen Rays on Normal and Vascularized Cornea of the Rabbit, ibid. **33**:549, 1950.

radium D and low voltage roentgen radiation. Scheie and co-workers [75c] have presented considerable data on low voltage irradiation of experimental and human eyes. They believe that low voltage irradiation may prevent corneal vascularization of corneal transplants and may be helpful in management of recurrent pterygiums, some types of vascularizing keratitis, vernal conjunctivitis and sclerosing keratitis.

CHEMICAL BURNS OF THE EYE

Grant [76] ably reviews the effects of various chemicals on the ocular structures. Ocular injuries from various chemicals differ widely in their rate of onset, symptoms and depth of involvement of the eye, and especially in respect to their prognosis. According to Grant, four major factors influence the severity of the chemical lesion of the eye.

1. The amount and duration of the exposure. The greater the concentration of the chemical and the longer the eye is exposed to it, the greater the ocular lesions. Some drugs produce no discomfort at the time of exposure, and therefore they may act undeterred for long periods of time, whereas others, such as lewisite (2-chlorovinyl dichloroarsine) produce immediate discomfort and the patient seeks help at once, thereby shortening the length of exposure. Splash injuries also are noticed and help is sought at once, so that the length of exposure is cut down.

2. Chemical reactivity of the injurious agent. Chemical compounds will react with different components of ocular tissue. They may alter or denature certain ocular structures or enzyme systems. With acids and alkalis, the severity of the injury is dependent largely on the concentration of hydroxyl or hydrogen ions and the duration of exposure. Alkalis denature the corneal mucoid, whereas acids primarily appear to cause denaturation of proteins.

Other compounds act as specific protein denaturants and selective enzyme inhibitors. Mustard gas (2-chloroethyl sulfide) and nitrogen mustards (methyl-bis, or tris-[2-chloroethyl]-amine) are examples of specific protein denaturants. However, mustard gas also has an effect on the enzyme hexokinase. Various methylating agents, such as dimethylsulfate, methyl iodide, methyl bromide, methyl salicylate and diazomethane, act similarly to the nitrogen and sulfur mustard compounds.

Arsenical compounds, such as lewisite, react with specific sulfhydryl groups in the cornea. Some of the notoriously injurious action on the eye of so-called indelible, or aniline, pencils is probably due to inactivation of vital corneal proteins, by binding of the acidic groups with certain basic dyes.

76. Grant, W. M.: Chemical Burns of the Eyes, J. A. M. A. **142**:152 (Jan. 21) 1950.

3. Physiochemical properties of the injurious agent. Typical of this group would be the wetting agents, or surface-active substances. These may change the surface properties of the epithelial barrier of the cornea and even cause actual disruption. The effect on the epithelial cells of the cornea may be similar to their lytic effect on blood cells. Substances which may produce injury to the cornea in this fashion are ordinary soaps, synthetic detergents and bile. Various organic solvents may produce damage by virtue of their physicochemical properties. Substances such as simple alcohol, ethers and ketones produce usually mild damage. Of course, the physical property of the compound may also determine its ability to penetrate into the cornea. The farther the compound penetrates, the more damage it may do.

The pathologic processes which may result from any of these chemical entities range from transient superficial disturbances of the epithelium to devastating damage to the entire anterior segment. The pathologic changes may be characterized by loss of epithelium, damage to the endothelium, denaturation of stromal constituents and iridocyclitis. Subsequently there will be edema of the stroma with infiltration of leukocytes and macrophages and invasion by new vessels and later by fibrous tissue.

Recommended therapy consists of immediate and thorough irrigation with innocuous fluids. The only specific agent recommended is 2,3-dimercaptopropanol (BAL) in arsenical burns. The remainder of the therapy is directed toward prevention of complications such as secondary infection, synechias and symblepharon. Later stage therapy may be given when the corneal lesion has become stabilized.

Other types of toxic effects on the eye have been reported in the past year, e. g., those of methyl alcohol,[77] maleic acid,[78] quinine,[79] tobacco [80] and digitoxin.[81]

Ethyl alcohol treatment of methyl alcohol poisoning appeared to be helpful in 1 of the cases reported.[77b] Walker [82] points out that methyl alcohol is readily absorbed from the gastrointestinal tract and is eliminated slowly. It is metabolized one tenth as rapidly as ethyl alcohol.

77. (*a*) Geserick, H.: Acute Methyl Alcohol Poisoning, Klin. Monatsbl. f. Augenh. **114**:502, 1949. (*b*) Agner, K.; Hook, O., and von Porat: The Treatment of Methanol Poisoning with Ethanol, Quart. J. Stud. on Alcohol **9**:515, 1949.

78. Winter, C. A., and Tullins, E. J.: The Irritating Effect of Maleic Acid and of Maleic Anhydride Upon the Eyes of Rabbits, Am. J. Ophth. **33**:387, 1950.

79. Das Gupta, B. K.: Quinine Amblyopia, J. Indian M. A. **18**:456, 1949.

80. Weekers, R.: Chronic Tobacco Poisoning, Rev. méd. Liége, **4**:573, 1949.

81. Sykowski, P.: Digitoxin Intoxication, Am. J. Ophth. **32**:572, 1949.

82. Walker, J. T.: Toxicology, New England J. Med. **242**:22, 1950; 56, 1950.

Toxicity may be due to formaldehyde and/or formic acid or to its effect on the oxidation-reduction enzyme system, but its mode of action is really not known. Administration of ethyl alcohol in moderate amounts may prevent the toxic effects of methyl alcohol. Sodium bicarbonate is also helpful in overcoming the acidosis produced.

CHOLINERGIC DRUGS

Studies have continued with the use of furfuryl trimethylammonium iodide (furmethide®) in glaucoma, and it is reported in the Russian literature to be effective in many eyes with this disease.[83]

SYMPATHOLYTIC AGENTS

Christensen and Swan [84] have demonstrated that a sympatholytic agent dibenamine® (N,N-dibenzyl-β-chloroethylamine hydrochloride) will lower intraocular pressure in eyes with acute glaucoma. This drug was effective in treatment of spontaneous narrow angle glaucoma, of glaucoma following atropine, of glaucoma following uveitis during the acute stages and of the chronic stages. The dose recommended is 4 to 5 mg. per kilogram of body weight given in 300 cc. of saline solution by intravenous drip for a period of one and one-half hours. The patient must be kept in bed for thirty-six hours. The mechanism by which this drug lowers intraocular pressure is not known. It is probably not through action on the iris, as in many of these eyes the iris did not move after the systemic administration of this drug. It is suggested that the lowering of intraocular pressure might be due to its effect on the formation of intraocular fluids. The drug is not free of toxic effects. One must be careful not to administer the drug to patients with cardiovascular disorders. Benzodioxan, another sympatholytic agent, has been found to produce encephalopathy.[85] Dibenamine® has produced auricular fibrillation.[86]

It is also known that in a number of patients resistance to the drug will develop rather quickly. A maximal effect on the intraocular pressure following a single injection of dibenamine® usually occurs within

83. Bolyak, B. L., and Volkov, V. V.: "Fouramon" in the Treatment of Glaucoma, Vestnik oftal. **28**:26, 1949. Rokitskay, L. V.: Action of "Fouramon" on the Retinal Edema of the Glaucomatous Eye, ibid. **28**:211, 1949. Vintserovich, N. A.: Action of "Fouramon" on the Glaucomatous Eye, ibid. **28**:29, 1949.

84. Christensen, L., and Swan, K. C.: Adrenergic Blocking Agents in the Treatment of Glaucoma, Tr. Am. Acad. Ophth. **53**:489, 1949.

85. Green, D. M., and Petershon, E. M.: Encephalopathy After Benzodioxan, J. A. M. A. **142**:408 (Feb. 11) 1950.

86. Hanno, H. A.: Auricular Fibrillation Following Administration of Dibenamine Hydrochloride, J. A. M. A. **141**:1144 (Dec. 17) 1949.

two to eight hours and lasts about twenty-four hours. In some cases the results may be fleeting.[86] Others have confirmed Christensen and Swan's observation with this drug.[87]

The method by which any miotic agent lowers intraocular pressure is not definitely known. The drug may work simply by a mechanical effect on the sphincter of the iris or on the ciliary muscle, or it may act through its influence on the vascular structures of the eye.[88] With an increase in the permeability of the small vessels within the eye there is greater chance for particles within the ocular fluids to pass back into the blood stream. In addition, dilatation of the vessels, with increase in permeability, would tend to bring the osmotic pressure of the aqueous humor toward equilibrium with that of the blood, the osmotic pressure of the aqueous being higher initially. However, as Grant [89] points out, there is at present no correlation of antiglaucomatous effectivity with intensity of effect on the barrier. In other words, sympatholytic drugs do not depress intraocular pressure in proportion to the degree they alter the blood-aqueous barrier.

PUPIL PHARMACOLOGY

It has been known since the experiment of Anderson that when the pupil has been denervated by removal of the ciliary ganglion the sphincter of the iris becomes sensitized to pilocarpine and fails to respond to physostigmine. This study has been repeated, and it has been shown that after removal of the ciliary ganglion in a cat the iris sphincter becomes sensitive to pilocarpine when it is administered by vein or instilled directly into the conjunctival cul-de-sac.[90] This sensitization

87. Beetham, W., in discussion on Grant.[89]

88. Cristini, G.: The Vascular Action of Pilocarpine, Eserine, Adrenalin and Atropine, and Their Influence in Primary Chronic Glaucoma, Brit. J. Ophth. **33**:228, 1949.

89. Grant, W. M.: Antiglaucomatous Drugs: Am. J. Ophth. **33**:124, 1950.

90. Neidle, E. A.: Pilocarpine Sensitization in Parasympathetically Denervated Pupil of the Cat, Am. J. Physiol. **160**:467, 1950; Response of Parasympathetically Denervated Cat's Pupil to Eserine, ibid. **160**:474, 1950. Scheie, H. G., and Ojers, G.: Choice of a Miotic Agent Following Retrobulbar Anesthesia, Am. J. Ophth. **32**:1369, 1949. Persichetti, C.: Effects of Some Miotics After Anesthetic Block of the Ciliary Ganglion, Gior. ital oftal. **2**:452 (Nov.-Dec.) 1949. Weekers, R., and Roussel, F.: Experimental and Chemical Studies of Pupillary Alterations Following Retrobulbar Alcohol Injection, Bull. Soc. belge d'opht. **91**:104, 1949; Ophthalmologica **118**:115, 1949. Joyle, G. E., and Oargand, A. G.: Pupillomotor Disturbances After Retrobulbar Injection of Alcohol, Bull. Soc. d'opht. Paris **1**:268, 1949. Bacq, Z. M., and Weekers, R.: Alterations in Pupillary Reactions Resulting from Cyclodiathermy and Retrobulbar Injections, Bull. Acad. roy. de méd. de Belgique **14**:183, 1949. Kornblueth, W.: Effect of Retrobulbar Alcohol Injection on the Eyes of Experimental Animals, Am. J. Ophth. **32**:781, 1949. Maumenee, A. E.: Retrobulbar Alcohol Injections, ibid. **32**:1502, 1949.

occurs immediately after extirpation of the ganglion but reaches its maximum in five to eight days. Sensitization of the denervated pupil is not altered by repeated local applications of pilocarpine or by previous intravenous injections of the drug. With the passage of time the sensitivity decreases, and by the two-hundredth day sensitivity returns to normal. This return can be explained by the regeneration of the postganglionic fibers. All reaction to physostigmine disappears by the seventh day after removal of the ganglion and seems to return in the majority of eyes in about thirty days.

This observation of a delay in the loss of response to physostigmine is fairly well known. It is postulated that enough acetylcholine is formed at the end of the cut nerve fibers by virtue of the irritation to stimulate the production of acetylcholine at the terminal branches in the sphincter of the iris, so that this muscle still responds to the administration of physostigmine and similar anticholinesterase drugs.

The recovery of function after ciliary ganglionectomy suggests that the postganglionic fibers are regenerated. If the third nerve is cut after the ciliary ganglion has been removed, regeneration is delayed. This suggests that the postganglionic fibers are regenerated from the preganglionic fibers. Is is also possible that the regeneration may occur from fibers of the fourth, fifth or sixth cranial nerve and that these nerves can supply cholinergic fibers to the denervated sphincter. It is also possible that accessory ciliary ganglions in the orbit may assume a functional role, supplying the sphincter, and that the sphincter itself may undergo some independent recovery.[9cb]

It has been demonstrated that retrobulbar injection of procaine or alcohol or cyclodiathermy temporarily denervates the pupil. Such injections appear to interfere with liberation of impulses along the parasympathetic postganglionic fibers, and probably sympathetic postganglionic fibers as well. Therefore, drugs such as pilocarpine and other cholinergic drugs are effective in constricting the pupil, whereas anticholinesterase drugs are not effective until the effects of procaine or alcohol have dissipated.[9cc-g] As Scheie and Ojers mentioned, this demonstrates the necessity of using a drug, such as pilocarpine, for constriction of the pupil in postoperative care in cases in which retrobulbar anesthesia has been employed.

Kornblueth has shown that retrobulbar injections of alcohol interfere with corneal wound healing. It also caused a drop in vitamin C content of the aqueous humor and a rise in glucuronidase activity of the ciliary body. The rate of flow of aqueous humor and the intraocular pressure fell and remained low for two to three weeks.

Maumenee was able to demonstrate the ability of retrobulbar injections of alcohol to lessen ocular pain and blepharospasm in blind eyes and in some with partial vision.

CYCLOPLEGIC AGENTS

Swan [91] has ably reviewed the role of choline esters in ophthalmology. He has found that their activity appears to be related to their surface activity. Surface-inactive choline esters act as miotics, and surface-active choline esters produce mydriasis and cycloplegia; of the surface-active choline esters that he has prepared, dibutoline sulfate (dibutylcarbamate of dimethylethyl-2-hydroxyethyl ammonium sulfate) seems the most useful. It is comparable in 5 to 7 per cent concentration to a 4 per cent solution of homatropine hydrobromide. It is an adequate cycloplegic for adults and may be used for this purpose in children when combined with atropine or scopolamine. The penetration of this drug through the cornea is not reliable, and some agent, such as a local anesthetic, should precede dibutoline into the cul-de-sac to facilitate penetration. One may use dibutoline sulfate for dilation of the pupil when an eye has become sensitized to atropine and related agents. However, it must be instilled very frequently to produce the desired effect in the presence of inflammation.

Gettes [92] has demonstrated that dibutoline sulfate combined with homatropine hydrobromide is an adequate cycloplegic for refraction in adults.

Homatropine hydrobromide, 2 per cent concentration, will produce a change in the area of angioscotoma.[93]

Cases of glaucoma precipitated by homatropine, as well as of glaucoma following oral administration of atropine,[94] have been reported.

ACTH AND CORTISONE

The startling results of the administration of 17-hydroxy-11-dehydrocorticosterone (formerly known as compound E and herein called cortisone) and pituitary adrenocorticotropic hormone (ACTH) in many rather different diseases have stimulated great interest in these substances. It has been well known for some time that when the adrenal glands are removed the animal or person dies. In order for patients who have suffered from Addison's disease to continue living, it is necessary that they have supplementary injections of adrenal cortex hormone. The

91. Swan, K. C.: Ocular Effects of Choline Esters, Arch. Ophth. **42**:709 (Dec.) 1949.

92. Gettes, E. C.: Dibutoline Sulfate: Comparative Clinical Study of Cycloplegic Effects, Arch. Ophth. **43**:446 (March) 1950.

93. Castagno, M. M.: Effect of Local Use of Homatropine Hydrobromide on the Normal Angioscotoma, Am. J. Ophth. **33**:367, 1950.

94. Allman, E. V., and Mossman, F. D.: Glaucoma and Orally Administered Belladonna, Northwest Med. **48**:245, 1949. Larmande, A. M.: Ocular Disturbances Due to Atropine Taken Orally or by Injection, Algérie méd. **52**:113-114, 1949.

medulla of the adrenal gland manufactures only one hormone, epinephrine. The cortex, however, turns out approximately twenty to thirty different compounds. These compounds have not all been isolated.

Kendall in 1935 isolated the first few granules of cortisone.[95] It was the fifth in a series of hormones that he had separated from adrenal cortex extract, and therefore it was called compound E. He showed that compounds A, B and E had some effect on metabolism and that compound E had a marked effect on muscular activity and apparently increased the animal's ability to resist exposure to cold, poisons and other physiologic stresses.

Hench [96] had noticed as early as 1929 that both pregnancy and jaundice decreased arthritic symptoms for temporary periods. As soon as the pregnancy was completed or the jaundice was gone the arthritis returned. He suggested that some antirheumatic factor was being produced in the body in greater quantities during pregnancy and in jaundice than normal. The adrenal glands were investigated, for it was known that under other conditions of stress, such as those imposed by anesthesia and bacterial invasion, these glands rapidly increased their secretion. With the availability of cortisone, the drug was tried on arthritic patients by Hench, Kendall, Slocumb and Polley,[97] with definite beneficial effect.

The anterior lobe of the pituitary produces, along with other hormones, a substance known as the adrenocorticotropic hormone, or, more simply, ACTH. This stimulates the cortex of the adrenal gland to produce cortisone, as well as other substances [98] (table 12). Hench

95. Mason, H. L.; Myers, C. S., and Kendall, E. C.: The Chemistry of Crystalline Substances Isolated from the Suprarenal Gland, J. Biol. Chem. **114**:613, 1936. Kendall, E. C.: Some Observations on the Adrenal Cortex Designated Compound E, Proc. Staff Meet., Mayo Clin. **24**:298, 1949. Mason, H. L.; Hoehn, W. M., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex: IV. Structures of Compounds C, D, E, F and G, J. Biol. Chem. **124**:459, 1938. Kendall, E. C.: The Adrenal Cortex, Arch. Path. **32**:474 (Sept.) 1941.

96. Hench, P. S.: The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, Ann. Int. Med. **7**:1278, 1934; The Potential Reversibility of Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **24**:167, 1949.

97. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone—Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis, Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181, 1949.

98. (*a*) Mason, Kendall and associates.[95] (*b*) Hench.[96] (*c*) Hench and associates.[97] (*d*) Li, C. H.: Society of Endocrinology, Lancet **1**:213, 1950. (*e*) Gray, G. W.: Cortisone and ACTH, Scient. Am. **182**:30 (March) 1950. (*f*) Heard, R. D. H.; Sobel, H., and Venning, E. H.: The Neutral Lipid-Soluble Reducing Substances of Urine as an Index of Adrenal Cortical Function, J. Biol. Chem. **165**:699, 1946. (*g*) Holtorff, A. F., and Koch, F. C.: The Colorimetric Estimation of 17-

and associates therefore tried ACTH for its antirheumatic effects and found that they paralleled those of cortisone in practically every respect.[87]

Selye [88e] found that the body responds in a general way to a variety of injuries, such as exposure to cold, burns, fractures, infections, poisons, terror and other emotional trauma. He could classify the reactions of the body into a three stage pattern, which he named the "general adaptation syndrome." Irrespective of the nature of the stress, the physiologic response of a healthy animal is always marked by three stages: (1) the alarm reactions, signaled by drastic physical changes; (2) the stage of resistance, in which these symptoms subside but the body is extraordinarily sensitive to other forms of damage, and (3) the stage of exhaustion. The tragic climax to prolonged stress occurs when the body runs out of its capacity for the defense reaction and dies. Selye

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Ketosteroids and Their Application to Urine Extracts, ibid. **135**:377, 1940. (*k*) Effects of Cortisone and Pituitary Adrenal Corticotropic Hormone, editorial, J. A. M. A. **142**:730 (March 11) 1950. (*l*) Elkinton, J. R.; Hunt, A. D., Jr.; Godfrey, L.; McCrory, W. W.; Rogerson, A. G.; and Stokes, J., Jr.: The Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, ibid. **141**: 1273 (Dec. 31) 1949. (*j*) Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Matieson, B. H.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950. (*k*) Randolph, T., and Rollins, J. P.: Relief of Allergic Diseases by ACTH in Proceedings of the First Clinical ACTH Conference, edited by J. Mote, Philadelphia, The Blakiston Company, 1950. (*l*) Rose, B.: Studies on the Effect of ACTH on Eosinophilia and Bronchial Asthma, in Proceedings of the First Clinical ACTH Conference, edited by J. Mote, Philadelphia, The Blakiston Company, 1950. (*m*) Thorn, G. W.; Bayles, T. B.; Massul, B. F.; Forsham, P. G.; Hill, R. S.; Smith, S., 3d, and Warren, J. E.: Medical Progress—Studies on the Relation of Pituitary Adrenal Function to Rheumatic Disease, New England J. Med. **241**:529, 1949. (*n*) Boland, E. W., and Headley, N. E.: The Effects of Cortisone Acetate on Rheumatoid Arthritis, J. A. M. A. **141**:301 (Oct. 1) 1949. (*o*) Ragan, C.; Grockoset, A. W., and Boots, R. H.: Effect of Adrenocorticotropic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **77**:41, 1949. (*p*) Forsham, P.: In discussion on Friedman, S.; Fersching, J.; Wang, C. C., and Smith, L. C.: The Effect of ACTH in Patients with Pulmonary Tuberculosis, Proceedings of the First Clinical ACTH Conference, edited by J. Mote, Philadelphia, The Blakiston Company, 1950. (*q*) Reiss, R.; Riggs, D. S.; Thorn, G. W., and Forsham, P. H.: Proceedings of the First Clinical ACTH Conference, edited by J. Mote, Philadelphia, The Blakiston Company, 1950. (*r*) Torda, C., and Wolf, H. G.: The Effects of Adrenocorticotropic Hormones on Pituitary Gland on Neuromuscular Function in Patients with Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **57**:137, 1944. (*s*) Stanbury, J.; Sprague, R. G., and Sofer, L. J.: In discussion on Torda and Wolf.[88r] (*t*) Randt, C. T.; Traeger, C. H., and Merritt, H. H.: Clinical Study of Effect of ACTH in Clinic Neurologic Disorders in Seven Patients, Proceedings of the First Clinical ACTH Conference, edited by J. Mote, Philadelphia, The Blakiston Company, 1950. (*u*) Mann, W. A., and Markson, B. E.: Case of Recurrent Iritis and Episcleritis on a Rheumatic Basis Treated with ACTH, Am. J. Ophth. **33**:459, 1950. (*v*) The Doctor's Dilemma, editorial, ibid. **33**:633, 1950.

found that the adrenal cortex played an important role in the defenses of the body. When it was defective, the alarm reaction was feeble. The animal passed rapidly to the stage of exhaustion. When the adrenal glands were entirely removed, resistance to stress practically disappeared and death came quickly.[95c] Selye also showed that when the response of the adrenal glands to stress goes wrong this response can lead to disease, such as arthritis and high blood pressure. His studies also indicated that two hormones from the cortex, one known as desoxycorticosterone and the other named compound S by its discoverer, T. Reichstein, were responsible for these abnormal changes. Further studies demonstrated that cortisone counteracted these hormones and caused the disease to disappear in animals. Thus, the adrenal

TABLE 12.—*Effects of ACTH in Experimental Animals*[94d]

1. Stimulates production or liberation of all adrenal steroids, androgens, estrogens, etc.	
2. Retards body growth—antagonistic to growth hormone of the anterior lobe of pituitary gland	
3. Alters nitrogen and potassium excretion	
4. Increases free amino acid content of plasma	
5. Produces glycosuria and hyperglycemia in some experimental animals	
6. Increases body fat	
7. Increases ketone bodies in urine and blood	
8. Diminishes plasma alkaline phosphatase	
9. Causes deterioration of chondrogenesis and osteogenesis of tibia	
10. Causes thinning of epidermis and atrophy of sebaceous glands and hair	
11. Causes involution of thymus and lymph nodes, with depletion and dissolution of lymphocytes	
12. Decreases circulating eosinophilic granulocytes	
13. Enhances work performance	
14. Improves resistance in normal rats to cold, starvation, etc.	
15. Produces inhibition of insulin effect on glycogenesis	Not in hypophysectomized animal
16. Produces inhibition of development of male accessory characters	Not in hypophysectomized animal

cortex can both cause the disease and cure it. Selye also demonstrated that the organism produces ACTH in response to stress or injury.

A number of diseases, because of certain common etiologic, pathologic, clinical and pharmacologic features, may be grouped together. Represented in this group of diseases are rheumatoid arthritis, serum sickness, periarteritis nodosa, disseminated lupus, rheumatic fever, dermatomyositis and scleredema. Histologically, they are characterized by collagen necrosis and are, therefore, diseases of the hyaluronate-containing tissues. They run a chronic relapsing course, may present manifestations in the joints and may show allergic features. Many of their clinical manifestations, such as (*a*) local inflammation, (*b*) fever, (*c*) changes in the leukocyte count, (*d*) increased sedimentation rate and (*e*) alterations in the albumin-globulin ratio, suggest a chronic infection, although no such an infection has ever been found. Because of the absence of signs of infection, the recent trend is to regard these features as due to primary disturbances in the immunity mechanism. A most important characteristic of this group of diseases is the fact that they can

be precipitated by a wide variety of unrelated harmful stimuli, such as infection, chronic fatigue, severe emotional strain, physical agents, drugs and injections of foreign protein. This feature can be explained by Selye's work.

The diseases resulting therefrom may be regarded as a disturbance in the adaptation of the animal to these harmful stimuli. Of importance is the observation of Selye that this abnormal phase of adaptation occurs only when the adrenal cortex is intact. It can be theorized that the transient, but beneficial, effect of such substances as salicylates, colchicine or protein shock therapy on arthritis, uveitis and various ocular diseases may be due to their ability to induce an outpouring of cortical steroid hormones.

Methods for measuring the amount of cortical hormones in solution were devised by Venning and others.[5,6,7] It has been shown in Cushing's disease that high quantities of the adrenal cortex hormones are secreted in the urine. This is to be expected, for Cushing's disease is characterized by overaction of the adrenal cortex. It has been shown that cortical hormones are in excess quantity in the urine of patients with burns and infections and after surgical operations.

Venning demonstrated that the cortical hormone output rose progressively during gestation and that in the eighth month it was equal to that of a victim of Cushing's disease. Venning also found that in the first three to five days of life the newborn infant has an extremely low supply of these hormones. The adrenal gland is not fully developed in unborn babies but matures within a few days after birth. This observation suggested that the poor resistance of newborn infants may be due to this deficiency. Venning showed in a woman that directly after an outburst of hysteria the cortical hormones, which are normally between 40 and 60 units, rose within twenty-four hours to 300 units. The cortical hormone level of another patient shot up to 250 units on receipt of news that her sister was dangerously ill. These measurements suggest that a mental or emotional upset is just as truly an injury to the body as the fracture of a bone, or burn, or bacterial infection.

ACTH has no effect if the adrenal glands are absent or atrophied, but increases the secretion, and perhaps the regeneration, of adrenal glands which are only sluggish or underdeveloped. However, in patients with defective adrenal glands cortisone will have to be used. If the adrenal glands are normal, either cortisone or ACTH may be used. Cortisone will supplement the body's natural output of cortisone, and ACTH will stimulate the adrenal glands to increase this natural output. In either instance the effect is to raise the concentration of cortisone in the blood stream and thus increase the resistance of the body to stresses of all kinds.

These drugs have undesirable physiologic effects, such as the rise in blood pressure, severe headaches, edema, excessive hair growth, cutaneous eruptions and, occasionally confused mental state. Desoxycorticosterone and Reichstein's compound S have been mentioned as possible causes of rheumatism. They seem to produce other disorders of connective tissue as well. Other hormone products of the adrenal cortex include a masculinizing hormone similar to testosterone, the pregnancy hormone progesterone, and corticosterone (Kendall's compound B), all of which are remarkably similar in structure to cortisone. Still another cortical product is compound F, the sixth hormone isolated by Kendall. The only structural difference between it and cortisone is the presence of an extra hydrogen atom in compound F. Tests show that compound F will suppress the symptoms of rheumatism quite as effectively as cortisone. Because of the size and complexity of the molecule of ACTH it has not been synthesized. It can be obtained only by extraction from pituitary glands, and it takes the pituitary glands of more than 500 hogs to provide 1 Gm. This is the approximate amount necessary to treat 1 patient with rheumatoid arthritis for twenty days.

The cortisone molecule is smaller than the ACTH molecule, and there is hope that it may eventually lend itself to full synthesis. It now requires the bile acid of 4,000 cattle to produce 1 Gm. of cortisone. The present production is about 200 Gm. per month. The cost of ACTH is about $200 per gram, and the cost of cortisone, approximately $150 per gram.[95f] One gram of cortisone is just enough to treat an arthritic patient for ten days.

One must know the unpleasant physiologic effects of long-continued treatment with cortisone or ACTH. These hormones are powerful agents which influence a wide variety of physiologic functions. The uncomfortable effects bear a relation to the size of the daily dose and the duration of the period of administration. Although some patients showed little or no intolerance even to fairly prolonged administration of cortisone or ACTH, in others one or more of all the clinical and metabolic features encountered in adrenocortical hyperfunction were observed in varying combinations.[95h] Prominent among these are rounding of the facial contour, mild hirsutism, acne, keratosis pilaris, muscular weakness, edema, amenorrhea, purplish cutaneous striations, impairment of carbohydrate tolerance, negative nitrogen balance and hypopotassemic alkalosis. In most cases the excretion of creatine and uric acid is increased. In some a negative balance of potassium is encountered. One might also watch for hypopotassemia associated with characteristic alterations of the electrocardiogram. Sodium and chloride excretion is variable. Usually reports show a retention of both sodium and chloride early in the period of administration of cortisone or ACTH, with increased excretion later. Increased excretion of calcium has been noted in some cases.

Study of the steroids in the urine suggests that the human adrenal cortex, when stimulated by pituitary adrenocorticotropic hormone, secretes mainly 17-hydroxycorticosterone, the compound designated by Kendall as compound F, rather than 17-hydroxy-11-dehydrocorticosterone (compound E, or cortisone). Evidence also suggests that cortisone on its administration is excreted in the urine to a small extent as 17-ketosteroid and corticosteroids, some unchanged cortisone being present in the latter fraction.

There is evidence that the function of the adrenal cortices in man is depressed, at least transiently, by cortisone. This might be a disadvantage for a patient confronted with a surgical operation or other stress, such as that imposed by an acute infection. On the other hand, overstimulation of the adrenal cortices by long-continued administration of large doses of pituitary adrenocorticotropic hormone might conceivably lead to their exhaustion, and thus to adrenal insufficiency. Both these agents appear to interfere with wound healing. The Mayo Clinic workers offer the suggestion that these undesirable effects should not be considered toxic reactions but should be called physiologic alterations. As noted in the editorial in *The Journal of the American Medical Association*,[99k] hormones are two-edged swords. Hormones such as testosterone or insulin when used for purposes other than substitution therapy may provoke disturbances which can be undesirable. The use of hormones as drugs requires careful consideration so that the specific disease process can be corrected without seriously upsetting normal physiologic mechanisms.

ACTH has been tried in the treatment of many types of disease. It has, of course, been evaluated in normal subjects, in order to determine what metabolic effects it has, and also in abnormal subjects, to determine the metabolic effects under such conditions as well.[99] It has been tried various endocrine abnormalities, collagen diseases,[99l] hypersensitivity

99. (*a*) Elkinton and others.[99d] (*b*) Sprague and others.[99j] (*c*) Randolph and Rollins.[99k] (*d*) Rose.[99l] (*e*) Thorn and others.[99m] (*f*) Boland and Headley.[99n] (*g*) Ragan and others.[99o] (*h*) Long, D. A., and Miles, H. A.: Opposite Activities of Thyroid and Adrenal Hormones in Allergic Hypersensitivity, Lancet, **1**:492, 1950. (*i*) Smith, R. T.: Testosterone, Pregnenolone and Irradiated Ergosterol in Treatment; Fitch, D. R.: Effect of Newer Steroids on Synovial Membrane Permeability and on Rheumatoid Arthritis; Hollander, J. L.: Experiments with ACTH and Cortisone, in symposium sponsored by the Philadelphia County Medical Society, College of Physicians of Philadelphia, March 8, 1950, on "The Present Status of Hormone Therapy in Rheumatoid Arthritis: Endocrine Aspects," edited by J. Lansbury. (*j*) Gordon, D. M., and McLean, J. M.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy in Ophthalmologic Conditions, J. A. M. A. **142**:1271 (April 22) 1950. (*k*) Olson, J. A.; Steffensen, E. H.; Margulis, R. R.; Smith, R. W., and Whitney, E. J.: Effect of ACTH on Certain Inflammatory Diseases of the Eye, ibid. **142**:1276 (April 22) 1950.

states,[98j-l] infections, malignant growths, mental disease, muscle diseases and demyelinating disorders, as well as various miscellaneous conditions. It is especially interesting to note the reported improvements in dermatomyositis, periarteritis nodosa, lupus erythematosus disseminatus and scleroderma. Relief in certain acute and allergic diseases has also been reported.

Rose's [98l] discussion is interesting in view of the fact that it has been known for some time that removal of the adrenal gland is followed by a rise in histamine content of tissues and blood. Apparently, the mechanism for destruction of histamine is impaired when the adrenal glands have been removed. If cortisone is administered, the tissue histamine and blood histamine concentrations decrease, and the mechanism for its destruction is improved. It is known also that pregnancy often clears up asthma. Rose studied 6 patients, measuring their nitrogen, sodium chloride and potassium balances and the urinary excretions of the ketosteroids, glycogenic corticoids, histamine and histidine. In all these patients definite improvement followed the use of ACTH. However, ACTH had no effect on skin tests, with their reacting allergens; i. e., the reactions to skin tests were the same after the administration of ACTH as before. Others have described an alteration in the reactions to skin tests during ACTH therapy.[98j] Forsham [98p] noted that ACTH decreased the reaction to purified protein derivative for fifteen days, for the duration of ACTH therapy, but the hypersensitivity reaction of the skin returned after administration of ACTH was stopped. The longest remission after cessation of ACTH therapy was one month. In every one of these subjects there were a measurable output of histidine and an excess of histamine in the urine before treatment. During ACTH therapy there were a marked output of histidine and a decided reduction of urinary histamine.

A few patients with hyperthyroidism [98q] associated with exophthalmos were treated with ACTH, and in the majority there was no change in the degree of exophthalmos. In 1 patient the exophthalmos that had developed after thyroidectomy improved temporarily with ACTH therapy. However, many of the patients with hyperthyroidism alone did show improvement with ACTH.

It was suggested some time ago by Torda and Wolf [98r] that the adrenocorticotropic hormone of the pituitary gland might have some benefit for patients with myasthenia gravis, on the basis of the following observations:

1. The immediate cause of the symptoms of myasthenia gravis is a decrease of acetylcholine.

2. Administration of ACTH increases acetylcholine synthesis in vivo.

3. Increase in the lymphatic tissue, i. e., round cell infiltration of various organs (mainly striate muscle) and hyperfunction of the thymus have been found in patients with myasthenia gravis. Tissue fractionation studies have shown that one of the sources of the substances that inhibit acetylcholine synthesis is the thymus. Administration of ACTH induces reduction in the mass of the thymus and the lymphatic tissue.

4. Removal of the pituitary gland in rats induces changes in the electromyogram that closely resemble abnormalities noted in patients with myasthenia gravis. The pituitary gland of several patients who died of myasthenia gravis showed accumulation of eosinophilic colloid material, suggesting altered function of the gland.

For this reason, Torda and Wolf continued their researches on the value of ACTH in myasthenia gravis and reported improvement of the clinical state and the performance of objective tests in 8 patients with myasthenia gravis after the administration of ACTH. The remission has been variable and incomplete and of uncertain, but considerable, duration. The results reported by other observers were not so favorable.[98a]

No significant improvement could be seen in patients with various types of neurologic disorders, including multiple sclerosis.[98i]

Reports are beginning to appear in the ophthalmologic literature and meetings of cases of ocular diseases treated with ACTH. At the New York meeting of the Eastern Section of the Association for Research in Ophthalmology in January 1950, Gordon and McLean reported on several instances of favorable results of ACTH in treatment of uveitis and other ocular disorders.[98j] At the meeting of Wilmer residents on April 19, 1950, McLean suggested the possibility of secondary glaucoma produced by ACTH therapy, possibly due to sodium retention and the holding of fluid in the tissues.

At the clinical conference on ACTH in October 1949, 2 cases of acute iritis and 1 case of interstitial keratitis were reported in which the course was favorably influenced by ACTH. McLean failed to observe any significant effect in a few cases of atypical interstitial keratitis. A case of recurrent iritis and episcleritis on a rheumatic basis favorably treated with ACTH was reported by Mann and Markson.[98q]

At the Wilmer residents' meeting in 1950 Woods reported benefit in cases of sympathetic ophthalmia. The results in retrolental fibroplasia have been uncertain. McLean had no success in therapy of advanced cataracts. A group of Detroit investigators [98k] found ACTH to be beneficial in inflammatory ocular conditions, particularly uveitis and keratitis. As a guide to the effects of ACTH almost all investigators have followed the eosinophilic granulocyte count. It is depressed by ACTH. The usual dosage has been administration of from 10 to 20 mg. every four to six hours. The total dosage varied from 185 to 432

mg., and administration was continued over a period of three to thirteen days.[99k] Higher doses were employed in some cases by the New York group.[99j]

We are all aware that these are exciting observations. As we gain further knowledge of the physiologic properties of ACTH, cortisone and other adrenal cortex extracts, we may have to change our concepts of disease. Certainly, great strides will be made in the next few years in our knowledge of hormones and of their physiologic properties. At the present time, studies are somewhat restricted by the limited supply of both these agents. This produces a "doctor's dilemma," which has been well expressed by Vail.[99v]

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

American Ophthalmological Society.—The Eighty-Sixth Annual Meeting of the American Ophthalmological Society was held at Hot Springs, Va., May 31 and June 1 and 2.

On the scientific program appeared a number of contributions of considerable clinical value and interest. Endothelial dystrophy of the cornea appears as congenital, familial and idiopathic, and the various types were described by Drs. Ralph I. Lloyd and Jesse Levitt, of Brooklyn. They presented their findings in a case of congenital endothelial dystrophy in a newborn child, in 3 cases of congenital dystrophy appearing in 2 brothers and a sister in adult life and in an isolated case of cornea guttata in a man aged 60.

Dr. David G. Cogan, of Boston, reported on "Ophthalmologic Surgery of Atomic Bomb Survivors in Japan." The study which formed the basis of this report is part of a long term project conducted by the Atomic Bomb Casualty Commission to investigate the medical and biologic effects of the atomic bombing in Japan. Cataract was the only significant ocular change found by the commission in a study of approximately 2,000 persons who were within the range of dangerous exposure from the explosion. It was apparent from this survey that these persons suffering serious injury to the eyes were within 3,000 meters of the epicenter of the explosion.

Dr. Harold G. Scheie reported his experimental study entitled "Ocular Hypertension Induced by Air in the Anterior Chamber." A discussion of this paper revealed considerable difference of opinion regarding the advisability of injecting air into the anterior chamber. Most discussers agreed that just the right amount injected after surgical procedures on the eyes would not result in glaucoma.

Three papers on glaucoma produced considerable favorable discussion of the mechanical establishment of transscleral channels for drainage of the anterior chamber. Dr. Peter C. Kronfeld and Dr. Isabelle McGarry, of Chicago, discussed the "Mode of Action of Iris Inclusion Operations." They applied spring pressure (dynamometer) to various portions of the eye in order to determine the patency of the scleral fistula after iris inclusion. Among the methods they used, and the one they reported on particularly, was the demonstration of filtration through the scleral fistula by comparing the decrease in ocular tension during application of a measured pressure on different parts of the eyeball with and without pressure applied simultaneously at the site of the fistula. Their experiments clearly demonstrated patency of the scleral fistula in the absence of pitting edema of the conjunctivas.

In "A Gonioscopic Study of Fistulizing Operations," Dr. Arthur G. DeVoe, of New York, came to the conclusion that the lowering of intraocular tension is not primarily the result of mechanical fistulization.

Dr. Paul A. Chandler, of Boston, discussed the methods of relieving malignant glaucoma, which he defined as a form of postoperative intraocular hypertension in which the anterior chamber never reforms and the tension steadily rises. He suggested removal of the lens as a means of lowering intraocular pressure.

While the use of cortisone (adrenal cortex extract; 17-hydroxy-11-dehydrocorticosterone) and adrenocorticotropic hormone (ACTH) has been limited to a number of clinical cases in a limited number of hospitals and clinics, the therapeutic effects of these drugs are beginning to be known through the reports of their use in various diseases of the eye. Dr. Alan C. Woods reported on the "Clinical and Experimental Observations of the Effects of Cortisone and ACTH in Ocular Diseases." Patients with uveitis of undetermined origin, with ocular tuberculosis, with interstitial keratitis and with some external inflammatory conditions of the eye were treated by intramuscular injection, by subconjunctival injection and by instillation into the conjunctival cul-de-sac. The immediate response was that of blocking inflammation, so that there were an appearance of improvement in the disease condition and a striking lessening of symptoms, such as pain and redness, in most cases. The proper dosage and methods of administration have yet to be worked out.

Dr. Alfred Cowan restated the definition of "Emmetropia" and described an emmetropic eye on the basis of pure physiologic optics. He pleaded for restriction in the use of the term "emmetropia" to its real meaning and decried the loose use of the term in some discussions and papers on modern refraction.

A case of "Ophthalmia Nodosa," a severe granulomatous inflammation of the eye due to the hairs of a caterpillar, was reported by Dr. Trygve Gunderson, of Boston, and Dr. Levon K. Garron, of Piedmont, Calif. Circumstances were such that the authors could make an extended study of the clinical and pathologic effects of caterpillar hairs in the eye of the patient and through experimental introduction of the hairs into the eyes of animals. An intractable granulomatous inflammation is caused by the entrance of the setae into the eye.

Dr. David O. Harrington, of San Francisco, described a new instrument for removal of cataract by the suction method and showed by means of still and motion pictures the "Dynamics of Phakoerisis" in the intracapsular extraction of cataract. By slow motion photography Dr. Harrington demonstrated clearly the movement of the lens capsule from the annulus of the lens toward the side where the suction cup is applied. This movement aids in the dislocation of the lens.

"Fundus Changes in Juvenile Diabetic Patients" were discussed by Dr. Lawrence T. Post and Dr. Arthur W. Stickle Jr., of St. Louis, and a paper on a similar subject, "Diabetic Retinopathy in Pregnancy," was given by Dr. William P. Beetham, of Boston. Drs. Post and Stickle reported on a series of about 40 juvenile diabetic patients who had been under observation for more than ten years. The progress of the changes in the fundus was carefully noted and correlated with the physical and physiochemical findings in these diabetic patients. The authors showed clearly that the changes in the fundus were progressive regardless of the degree of control of sugar in the blood

and urine. The severity of the changes in the fundus is a function of the duration of the disease rather than an indication of the severity of the other symptoms of diabetes.

Dr. Beetham reported on the ophthalmic conditions in a series of diabetic pregnant women studied by Dr. Priscilla White, of the Joslin group. An attempt was made to evaluate the effect of pregnancy on women with diabetic retinopathy and to ascertain the prognostic significance of retinopathy as regards mother and fetus.

"A Familial Type of Bilateral Crystalline Dystrophy of the Cornea" appearing in two generations of the same family, 18 of whom were examined, was reported by Dr. W. E. Fry and Dr. William E. Pickett, of Philadelphia. The crystalline deposits in the cornea were found in 9 of the 18 persons examined. These deposits were not accompanied with inflammatory changes, nor did any other symptoms appear except in the older members, whose visual acuity was slightly reduced. The probable cause of the peculiar bluish green crystalline deposits is not explained.

"Experimental Studies on Early Lens Changes After Roentgen Irradiation" were reported by Dr. Ludwig von Sallmann, of New York. This work is a part of a broad experimental study in the production of cataract by short waves.

The danger of foreign substances entering the anterior chamber of the eye during intraocular surgical procedures was stressed by Dr. Derrick Vail, who read his paper on "Lint in the Anterior Chamber Following Intraocular Surgery." In the discussion evoked by this paper, it was generally agreed that small particles of lint, talc, metal plating from instruments and other small foreign bodies were not infrequently found in the wound and anterior chamber after intraocular operations. Eyelashes and droplets of ointment are occasionally found within the anterior chamber. Many methods of avoiding the entrance of foreign bodies into the eye during operation were proposed, among them the discontinuance of the use of talc on rubber gloves and the dipping of instruments into benzalkonium (zephiran®) chloride solution before introduction into the eye. Dr. Verhoeff stated that the use of rubber gloves was not necessary, or even desirable, in cataract surgery.

A preliminary report on the technic of "Total Penetrating Keratoplasty" was given by Dr. Ramon Castroviejo, who described the results in the transplantation of the entire cornea in cases of total leukoma. In some cases removal of the entire iris, along with the cornea, was necessary because of adhesions of the two layers, and even in such cases useful vision was restored. This operation seems to be indicated as a last resort in those cases in which other types of keratoplasty give poor results.

Dr. Arno E. Town, of New York, and Dr. A. E. Rakoff reported on a series of studies of the "Relationship of the Endocrine Glands to Cataract." Dr. Rakoff, of the section on endocrinology at Temple University School of Medicine, discussed at length the extensive studies in regard to patterns of endocrine dysfunction that have been made on patients who have cataract. They described their methods of examination and evaluation of endocrine dysfunction and compared

their findings in patients with cataract with those in patients who did not have cataract. The results of their studies were of sufficient interest to warrant further work along this line.

Pan-American Congress of Ophthalmology.—The Pan-American Congress of Ophthalmology, sponsored by the Pan-American Association of Ophthalmology and the National Society for the Prevention of Blindness, met March 26 to 30 at Miami Beach, Fla. Over 500 persons were present from all over the United States, Canada, Mexico, Cuba, Santo Domingo, Puerto Rico, the Central American countries, Venezuela, Peru, Chile, Argentina, Uruguay and Brazil. The official reception was held on Sunday afternoon. The complete program of the Congress was printed in the March issue of the ARCHIVES, pages 560 to 565. Among the actions taken at the meeting was the resolution to establish a station for the standardization of tonometers in Latin America. This station, sponsored by the Pan-American Association of Ophthalmology, is set up in São Paulo. The members of the Congress were all pleased with the arrangements made for their entertainment and convenience. At the conclusion of the meeting many of the Latin-American ophthalmologists accepted an invitation to visit a number of ophthalmologic clinics in the United States and Canada.

GENERAL NEWS

Training Course for Orthoptic Technicians.—A nine month course for the training of orthoptic technicians will begin on Oct. 2, 1950, under the auspices of the George Washington University School of Medicine. Application should be made to Dr. Ronald A. Cox, Department of Ophthalmology, George Washington Hospital, 901 Twenty-third Street, N. W., Washington, D. C.

Book Reviews

Practical Neurological Diagnosis. Fourth edition. By R. Glen Spurling, M.D., Price, $5. Pp. 290, with 118 illustrations Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This is a small textbook (290 pages), giving instructions on how to conduct a neurologic examination and how to interpret the findings. It is well illustrated and contains a number of useful aids, such as a glossary of terms, a table listing cerebrospinal fluid findings in various conditions and a series of roentgenologic pictures of the skull and spinal column. The material is presented succinctly according to anatomic subdivisions, with little or no discussion of controversial issues and a minimum of references.

The book is intended for, and is admirably suited to, the student. For those who already have a considerable familiarity with the subject it will be found insufficient, and some aspects of it may seem objectionable. Thus, from the ophthalmologic point of view the following objections may be noted (in the opinion of the reviewer): The illustration selected to show the eye (fig. 1) depicts a pencil of light undergoing absolutely no refraction! The statement that sparing of the macula is due to its wide representation in the brain does not coincide with the accumulating evidence that the macula is represented discretely at the posterior pole. The ophthalmoscope is described as being "indirectly lighted," whereas the illustration is that of "direct ophthalmoscopy." Papilledema is said to be due to venous congestion, whereas it is known that complete venous occlusion is accompanied with only mild papilledema. The diagram of actions of the extraocular muscles (fig. 11) has the objectionable feature (and the author is not alone in this) of indicating the vertical muscles as acting in oblique directions. The listing of signs and symptoms of Wilson's disease contains no reference to the pathognomonic Kayser-Fleischer ring of the cornea.

These objections, nevertheless, are minor, and similar ones may be found to any text which encompasses such a large field in such a small space. The fact is that this book, in the opinion of the reviewer, can be highly recommended to those for whom it is intended, namely, "students and practitioners who desire to become more proficient in the recognition of neurological disorders"; and this should include most ophthalmologists.

Obituaries

HARRY FRIEDENWALD, M.D.

1864-1950

Harry Friedenwald, that master of Israel, as well as of ophthalmology, died on April 8, 1950. He was born in Baltimore, Sept. 21, 1864, the son of Dr. Aaron Friedenwald, for years distinguished professor of ophthalmology in Baltimore.

Dr. Friedenwald was educated at the school of Baltimore and the City College, and later at Johns Hopkins, from which university he received an A.B. degree in 1884. He proceeded to the College of Physicians and Surgeons, Baltimore, graduating as Doctor of Medicine in 1886. After serving the term of internship at the City Hospital, he went to Europe, becoming attached to Hirschberg's clinic in Berlin. He continued abroad for three years, serving for a time in Politzer's Otological Clinic, in Vienna.

Returning to America in 1890, he began practice with his father in Baltimore. At about this time Dr. William Welch was creating the department of pathology at Johns Hopkins Hospital in the recently organized School of Medicine. Friedenwald joined him and served under him for several years, thus laying the foundation of his studies in pathology of the eye—the results of which he so fully reported in after years. His association with Welch developed into a deep friendship, which continued unabated as long as "Popsy" lived.

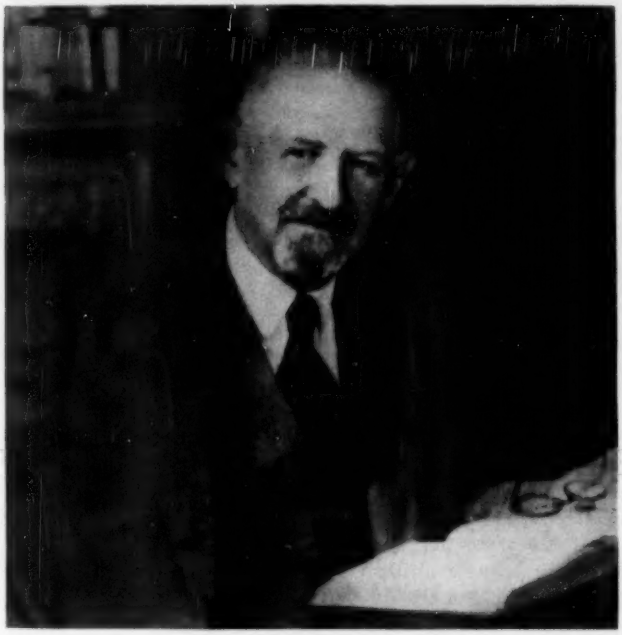
Dr. Friedenwald married Miss Bertha Stern in 1892. Two children were born to this devoted union, a daughter, and the son Jonas, who thus becomes the third generation of a distinguished medical family serving the community. It might be noted in this connection that Julius Friedenwald, Harry's brother, also entered medicine and was one of the inaugurators of gastroenterology in this country.

Friedenwald's practice began to increase, and his publications soon appeared, contributing on various aspects of ophthalmology and adding to the science year by year. He was associate professor of ophthalmology at the College of Physicians and Surgeons from 1894 to 1902, and, at the death of his father, professor from 1902 to 1929, the College having been merged with the University of Maryland. In 1930, he gave the Doyne Memorial Lecture at the Ophthalmological Congress of Oxford.

His association with the various medical organizations, both national and foreign, was intimate and honorable. Besides the chairmanship of the Section on Ophthalmology of the American Medical Association, he

was president of the American Ophthalmological Society in 1937, and as such he delivered the historical address at the seventy-fifth anniversary of the founding of the society.

All his days he was immersed in medicine; indeed, when I visited him a month before the end, he showed a keenness in discussing with me certain aspects of today's activities that showed to me the comprehension of his knowledge.



HARRY FRIEDENWALD, M.D.

1864-1950

In contemplating the facts of Harry Friedenwald's position in American medicine, one naturally harks back to the incidents of the inception of his career. His father had served in von Graefe's clinic when Liebrich and Schweiger were the master's assistants. Graefe was then imparting his immortal teachings on glaucoma. Medicine in Berlin was still under the influence of Johannes Müller, and of Virchow and DuBois-Reymond, who had learned from Helmholtz how to solve the problem of diseases of the eye by the use of the ophthalmoscope.

When Dr. Friedenwald became attached to Julius Hirschberg's *Augenheilanstalt*, he became imbued with the principle that the present depends on the past and that a knowledge of the history of the science should be learned in order to make one the servant of the present. Hirschberg was then gathering his materials for his "History of Ophthalmology," and one must recall that when Friedenwald was serving at Hopkins, Osler was exercising his influence over that brilliant group to become interested in the history of medicine.

In 1896 Dr. Friedenwald accompanied his father to Philadelphia, where, at the Dropsie College, he listened to his father's address on "The Contribution of the Jews to the Science of Medicine." He became so inspired that from that time many of his hours were occupied with thoughts of those contributions. Henceforth, he began to gather books and other literary publications, which served as the foundation of that which is unique in the history of medicine. The result is a priceless collection of books, manuscripts and incunabula dealing with all aspects of Jewish medicine. Harry Friedenwald was not merely a book collector but a studious reader and writer about the works he had gathered. From that library he always freely and generously lent works to others who evinced interest in these subjects.

His accounts of the Jews in medicine he gathered together in two volumes, entitled "The Jews and Medicine: Essays," published by the Johns Hopkins Press, 1944. The catalog is extensive and includes the names of ophthalmologists of Europe, Arabia and America. This library has been donated to the Hebrew University in Palestine.

Until his father's death, in 1903, he uninterruptedly devoted himself to his practice. But as Aaron Friedenwald had been a leader in the Jewish community in Baltimore, the leadership fell on him. The duties connected with that service were performed with great dignity and a sense of dedication. His position was animated by a sense of trust, not only for the Jews of America, but for those of Palestine. For several years he was president of the American Zionist Organization, devoting himself to it practically all his latter years.

It is an honor to have been invited by the editor to prepare this brief survey of the life and works of so outstanding a personality as Harry Friedenwald, whose scholarly knowledge was manifested with modesty and whose friendship was given with a loyalty and generosity that marked him as one unique in this generation.

BURTON CHANCE.

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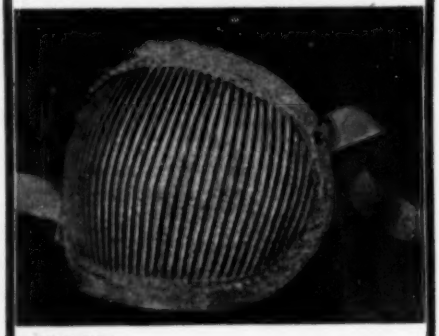

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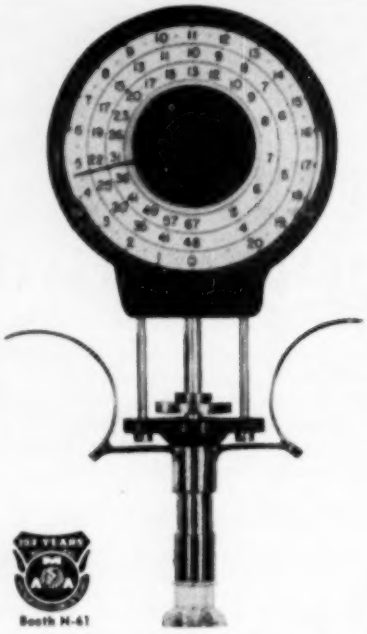

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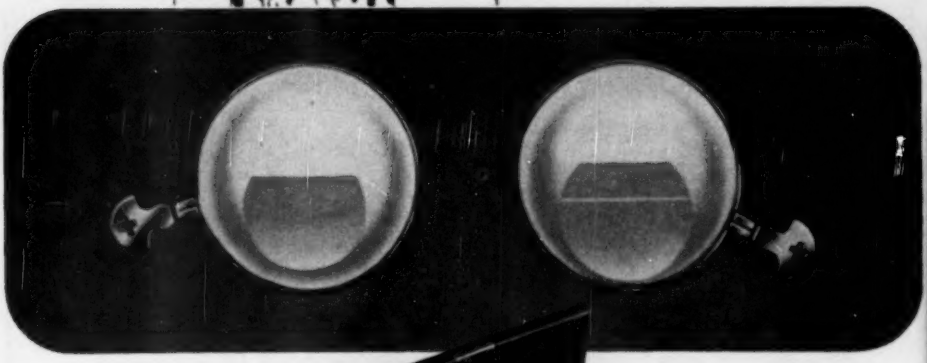

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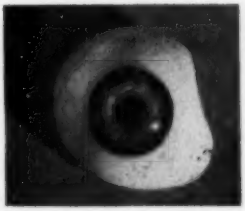

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CONTENTS

PAGE

Incision and Closure of the Wound in Cataract Operations: A Study of the Graefe Knife Versus the Keratome-Scissors Incision and a Method of Suture of the Deep Wound. Frederick Allison Davis, M.D., Madison, Wis. 175

Management of Strictures of the Lacrimal Canaliculi with Polyethylene Tubes. John W. Henderson, M.D., Rochester, Minn. 198

Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes. W. Morton Grant, M.D., Boston 204

A Unified Concept of Aqueous Humor Dynamics and the Maintenance of Intraocular Pressure: An Elaboration of the Secretion-Diffusion Theory. V. Everett Kinsey, Ph.D., Boston 215

Ocular Findings in the Newborn Infant: A Preliminary Report. Robert R. Chace, M.D.; Katharine K. Merritt, M.D., and Marjorie Bellows, M.S., New York 236

Cervical Sympathectomy in Nonsyphilitic Interstitial Keratitis with Vestibuloauditory Symptoms: Report of a Case. John T. Ronson, M.D., Tacoma, Wash. 243

Retrolental Fibroplasia as a Syndrome: Pathogenesis and Classifications. Parker Heath, M.D., Boston 245

Results of Operation for Cataract with Primary Glaucoma. Otis S. Lee, M.D., and Jack E. Weir, M.D., Iowa City 275

Migrainoid Headaches: Their Ocular Manifestations. Hugh C. Donahue, M.D., Boston 285

CLINICAL NOTES:

A New Instrument for Lamellar Keratoplasty. R. H. Bock, M.D., Geneva, Switzerland 293

ANNUAL REVIEWS:

Pharmacology and Toxicology: Review of the Literature. Irving H. Leopold, M.D., Philadelphia 300

NEWS AND NOTES 349

BOOK REVIEWS 353

OBITUARIES:

Harry Friedenwald, M.D. 354